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of the

CHEST

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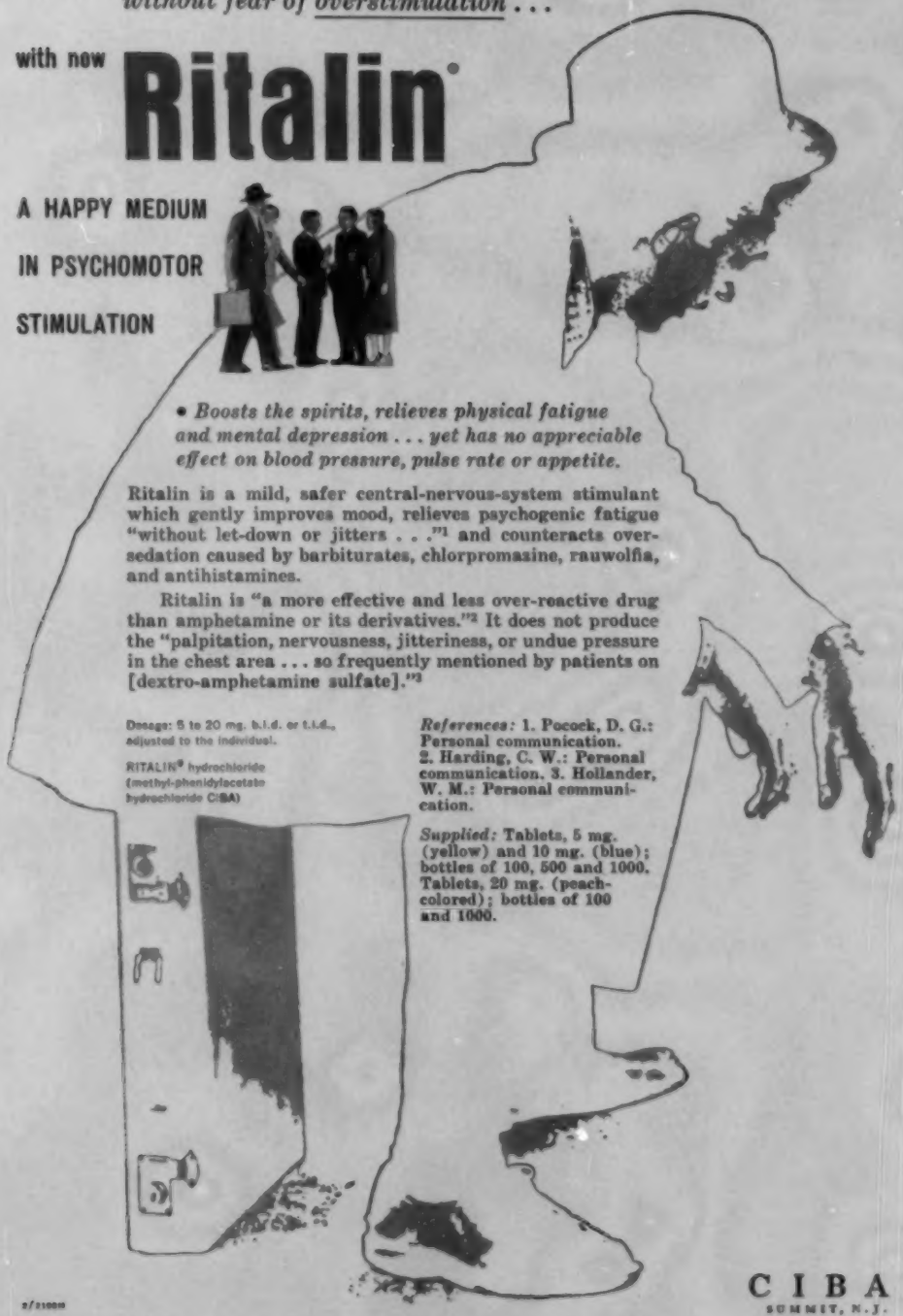

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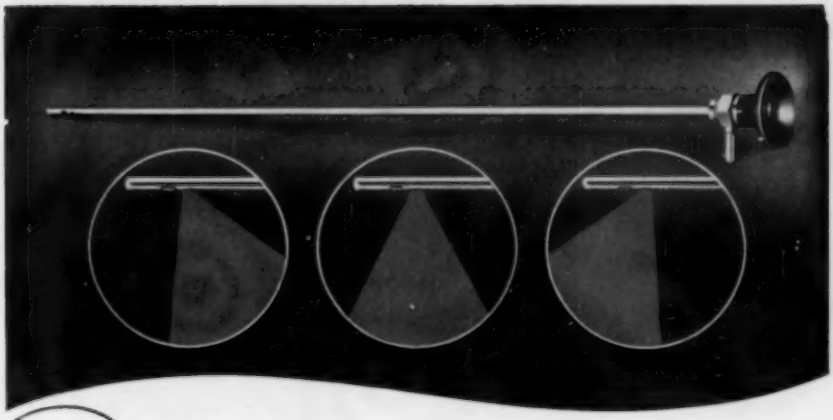

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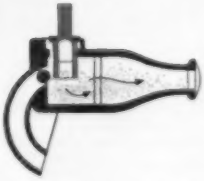

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CONTENTS

THE TREATMENT OF HUMAN PULMONARY TUBERCULOSIS WITH CYCLOSERINE: PROGRESS REPORT 241
Israel G. Epstein, M.D., K. G. S. Nair, M.D., and Linn J. Boyd, M.D., New York, New York

COR PULMONALE: ITS DIAGNOSIS AND MANAGEMENT 258
George C. Griffith, M.D., Los Angeles, California

THE HANDLING OF THE POOR RISK PATIENT WITH PULMONARY TUBERCULOSIS: ANTIMICROBIAL THERAPY, CARDIO-PULMONARY FUNCTION AND SURGERY 266
A. J. Kukral, M.D., John B. Grow, M.D., Gardner Middlebrook, M.D., and Sidney H. Dressler, M.D., Denver, Colorado

SARCOIDOSIS: PULMONARY AND SKIN STUDIES BEFORE AND AFTER ACTH AND CORTISONE THERAPY 277
A. Salomon, M.D., B. Appel, M.D., S. F. Collins, M.D., J. A. Herschfus, M.D., and M. S. Segal, M.D., Boston, Massachusetts

PULMONARY EMPHYSEMA, CARDIO-RESPIRATORY DISTURBANCE 292
Hurley L. Motley, M.D., Los Angeles, California

THE SELECTION OF CASES OF CORONARY HEART DISEASE SUITABLE FOR SURGICAL TREATMENT 305
N. A. Antonius, M.D., Ralph Miller, M.D., A. D. Crecca, M.D., and L. G. Massarelli, M.D., Newark, New Jersey

THE PLEURAL FORM OF PRIMARY CANCER OF THE LUNG 314
G. Babolini, M.D. and A. Blasi, M.D., Naples, Italy

BACTERIOLOGIC DIAGNOSIS OF TUBERCULOSIS IN MENTALLY ILL PATIENTS 324
E. Darzins, M.D. and T. M. Vitols, M.D., Anoka, Minnesota

SPONTANEOUS PNEUMOHEMOTHORAX 329
John J. Walsh, M.D., New Orleans, Louisiana

THE ROLE OF COUNSELING PSYCHOLOGY IN A TUBERCULOSIS HOSPITAL 336
Andrew W. Foley, Ed. D., Walla Walla, Washington

EDITORIAL: THE OVERALL EFFECT OF ANTIMICROBIAL THERAPY ON THE TUBERCULOSIS PROGRAM 346
Henry C. Sweany, M.D., Mt. Vernon, Missouri

THE PRESIDENT'S PAGE 350

FOURTH INTERNATIONAL CONGRESS 351

22ND ANNUAL MEETING 352

COLLEGE CHAPTER NEWS 353

OBITUARY: Alfred L. Kruger 356

CALENDAR OF EVENTS xxv

MEDICAL SERVICE BUREAU xxv

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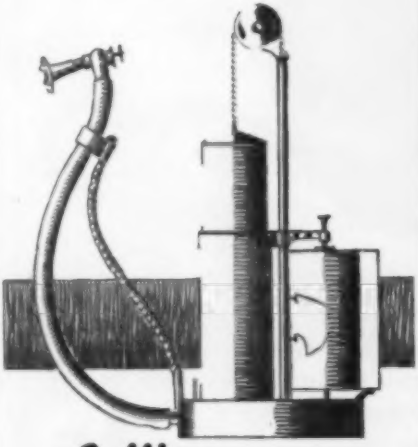

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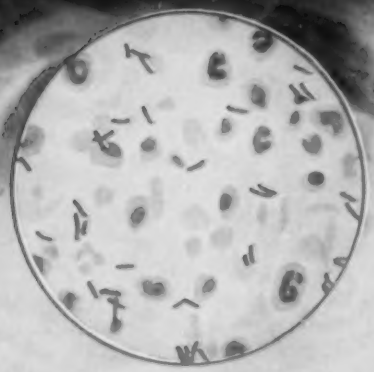

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by 1. Shubin, H., and Heiken, C. A.
2. Morton, R. F.; LaCaille, R. A.; Gold, A., and Prigot, A.
3. Payne, H. M.; McKnight, H. V., and Harden, K. A.

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A Laboratory and Clinical Report on Adrenosem® Salicylate

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History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam[1] in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"[2] enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. . . . One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.[2-7]

(* U.S. Patent 2,581,850)

Sherber, in an early study,[3] concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted, and is superior to any similar material that is now available."

He continues, "From our experience it appears that adrenochromazone complex is indicated in preventing vascular accidents incident to hypertension; in maintaining small vessel integrity; in the preoperative preparation where oozing from a vascular bed is anticipated, as in tonsillectomies, adenoidectomies and prostatectomies; and as an adjunct in the treatment of bleeding from such surgical procedures."

Adrenosem Salicylate may be administered simultaneously (but separately) with any type of anesthetic, anticoagulant, or vitamin K and heparin.

A Unique Systemic Hemostat

Clinical investigators[3-7] are in agreement that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeability and by promoting the retraction of severed capillary ends. It aids in maintaining normal capillary integrity by direct action on the intercellular "cement" in capillary walls. The interesting work of Fulton[5] confirms this. Adrenosem Salicylate, since it is not a vasoconstrictor, has no effect on large severed blood vessels and arterioles.

Adrenosem Salicylate is being used both prophylactically and therapeutically in thousands of hospitals, and in virtually every type of surgical procedure. It has also proved most useful in dental surgery.[7]

Owings reported on the use of Adrenosem Salicylate in controlling postoperative adenoid bleeding in 102 cases.[4] "We have used 2½ mg.

(½ ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from previous records, without Adrenosem Salicylate medication.

Peele reports on the use of Adrenosem Salicylate in treating 178 patients with 24 different conditions.[5] The drug was first used to control postoperative hemorrhage from the adenoid region. He adds: "The results were so dramatic that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagolic procedures, to treat postoperative hemorrhage from the tonsil and adenoid regions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate in controlling bleeding and oozing in 330 patients is reviewed by Bacala.[6] "Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely benefited by this metabolic hemostat, making a diminution of the control incidence of posttonsillectomy bleeding of 19.8% down to 7%. It has also been found useful in gastro-intestinal bleeding, cataract extraction, epistaxis, incisional seepage, trans-urethral prostatectomy, menometrorrhagias, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and prevention of capillary hemorrhages during hedulin or dicumerol therapy."

Side Effects

All investigators concur that, at recommended dosage levels, Adrenosem Salicylate is free from toxic effects. No cumulative effects attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."[5]

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with:
tonsillectomy, adenoidectomy and
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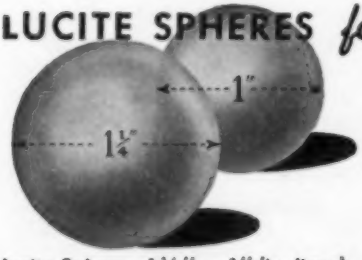

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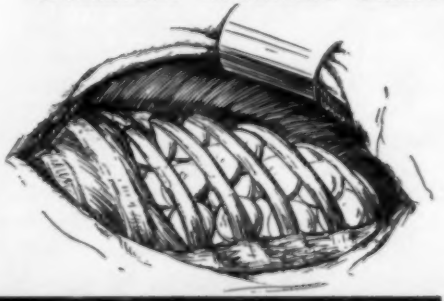

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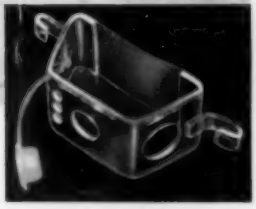

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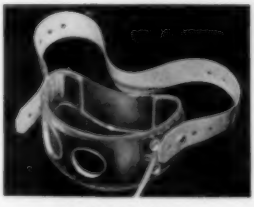

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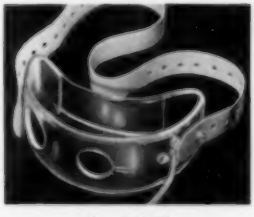

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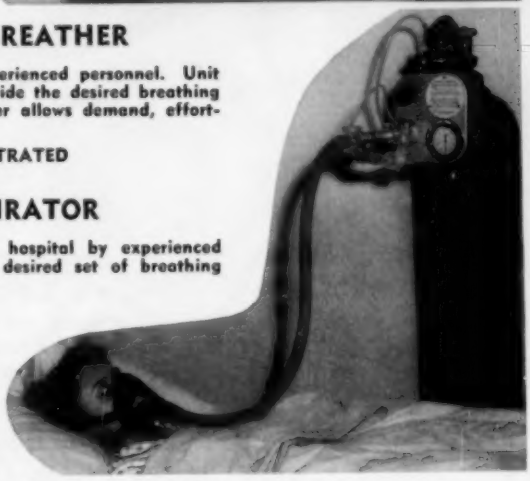

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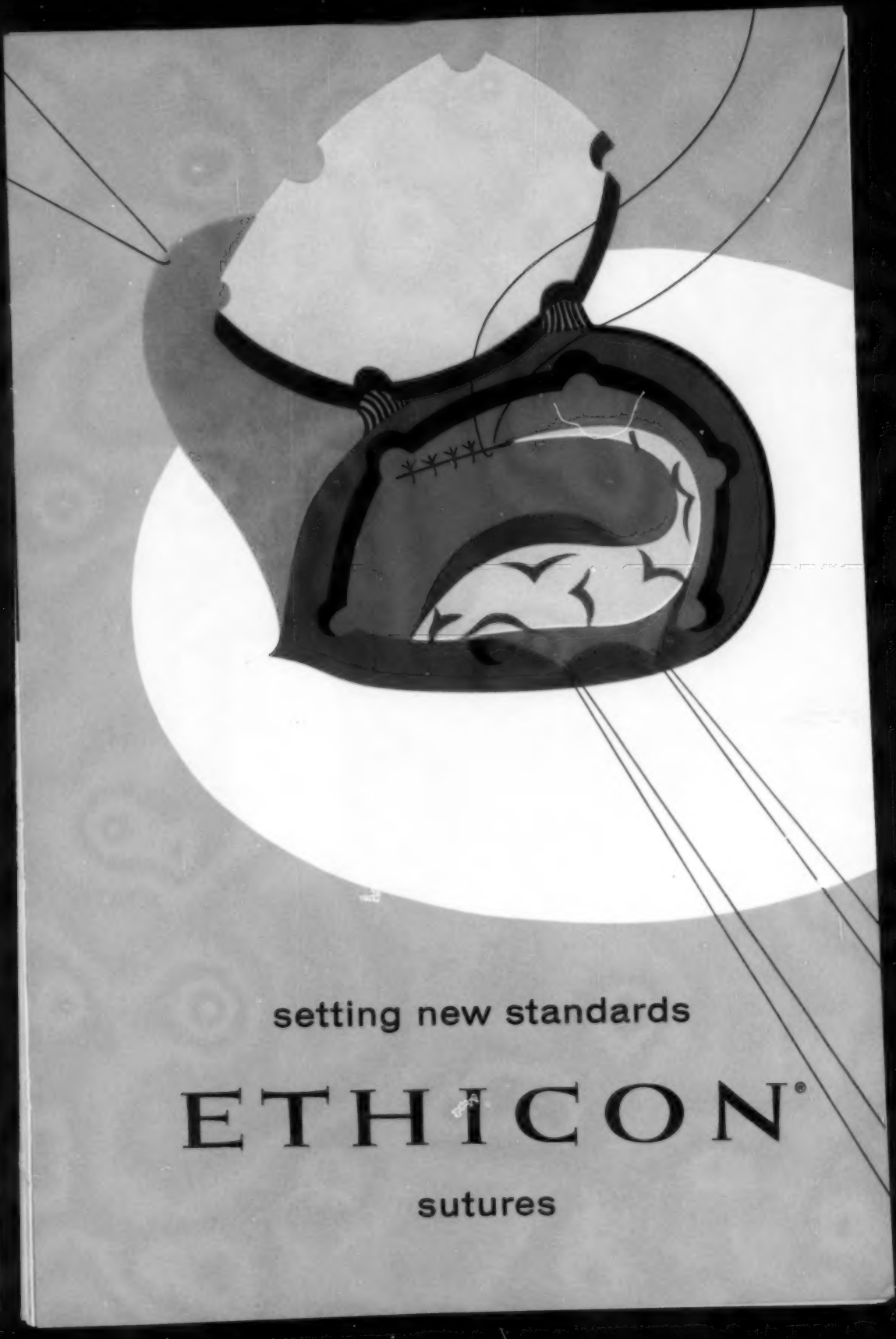
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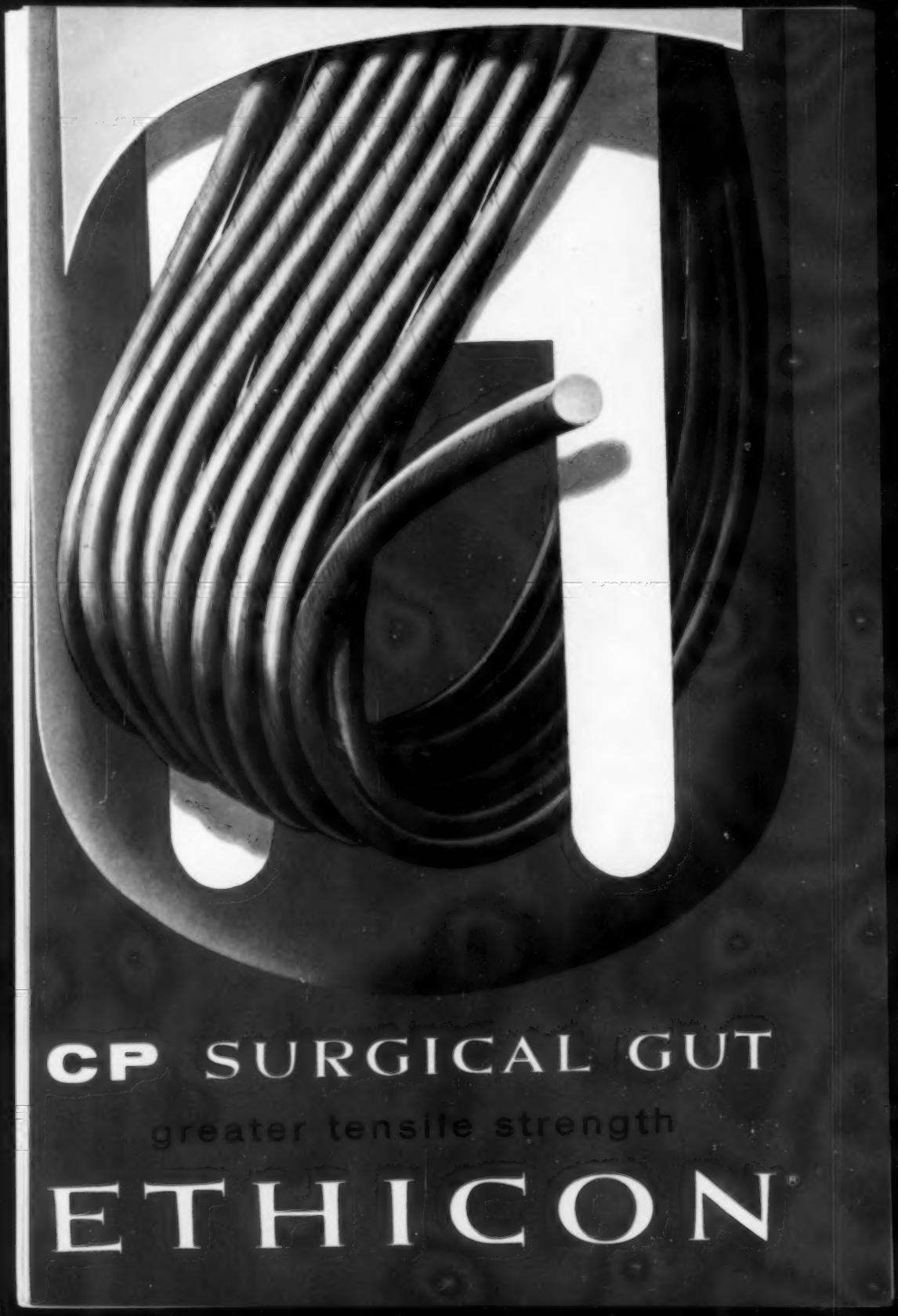
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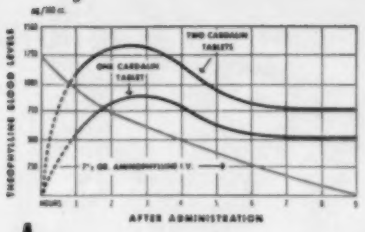

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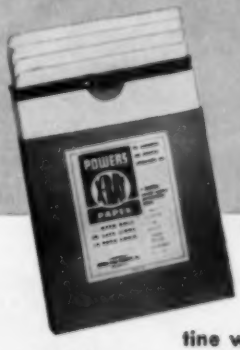

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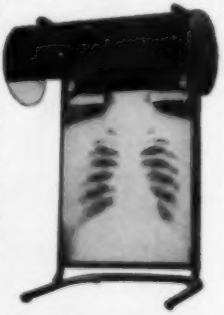

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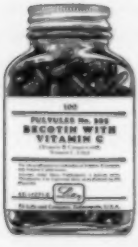

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DISEASES of the CHEST

VOLUME XXIX MARCH, 1956 NUMBER 3

The Treatment of Human Pulmonary Tuberculosis With Cycloserine:* Progress Report**

ISRAEL G. EPSTEIN, M.D., F.C.C.P., K. G. S. NAIR, M.D.
and LINN J. BOYD, M.D., F.A.C.P.

New York, New York

The discovery that streptomycin is an efficient antituberculosis drug revolutionized the treatment of pulmonary tuberculosis and has generated considerable optimism in regard to the outcome of this disease. Together with INH (isoniazid) or PAS (para-aminosalicylic acid), it has been instrumental in saving innumerable lives. By promptly clearing the sputum of tubercle bacilli, it has made prolonged hospitalization unnecessary and has lessened the number of subjects who would otherwise have become infected by contact with the patient. The chronic toxicity of streptomycin for the eighth nerve made the discovery of isoniazid doubly welcome, because the drug was not very toxic and because it proved effective in streptomycin-resistant cases. However, the rapid development of resistance by the tubercle bacilli to both streptomycin and INH has limited the usefulness of the drugs for a goodly proportion of cases.

PAS, with its mild antituberculosis effects and its ability to delay the development of resistance to the other antimicrobial agents, extended the usefulness of both streptomycin and INH. The eventual emergence of resistance to the antimicrobial agents, despite the use of PAS, and the development of eighth nerve involvement, despite the use of reduced doses of streptomycin, left a hiatus in the treatment of tuberculosis for which there was no effective remedy.

With the passage of time there has been an ever-increasing number of patients in sanatoria who have reached a limit of improvement with present antimicrobial therapy, and who, although they may retrogress upon discontinuance of treatment, do not continue to improve with it. For these reasons we were happy to have the opportunity to try the new antibiotic, cycloserine, in the treatment of a group of chronic cases who had reached a *status quo* with the other antimicrobial agents.

A preliminary report on the use of cycloserine in the treatment of human pulmonary tuberculosis has been given elsewhere.[1, 2] Up to that time cycloserine had been used on 37 cases, eight of whom were acute, previously untreated, and 29 chronic and clinically resistant to other antimicrobial

Department of Medicine, New York Medical College, and the Tuberculosis Division, Metropolitan Hospital, New York, New York.

*Manufactured by Commercial Solvents Corporation. The trade name of Eli Lilly & Co. for cycloserine is 'Seromycin'.

**Read as part of a symposium, 21st Annual Meeting of the American College of Chest Physicians, Atlantic City, New Jersey, June 4, 1955.

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agents. The present report gives follow-up data on these patients, as well as data on additional cases treated as cycloserine became increasingly available.

Cycloserine is a broad-spectrum antibiotic, the biological properties of which were reported by Welch et al.[3] During the laboratory investigation of this drug there developed a discrepancy between its relatively weak *in vitro* antibiotic activity and its virtual ineffectiveness in treatment of induced disease in animals, especially as regards tuberculosis.[4] However, cycloserine has been shown to have rather satisfactory clinical activity in tuberculosis,[1, 3] and in a variety of urinary infections.[5, 6] Welch[3] has suggested that cycloserine may owe its marked antibiotic activity to its small molecule (M.W. 102), enabling it to diffuse readily into various tissues and body cavities, and perhaps to other factors not directly related to its *in vitro* antibiotic activity. Possibly cycloserine is chemically modified within the human to a more active form. This would explain its superiority in man if one assumes, without basis, that the same conversion does not occur in the lower animals. Any high degree of conversion is unlikely, however, because over 70 per cent of ingested cycloserine appears in the urine as such. Because of its chemical resemblance to the amino acid, serine, it has been suggested that cycloserine may act by interfering with some enzyme system, or by blocking a metabolic pathway common to the tubercle bacillus and other sensitive bacteria.[3] The elucidation of the mode of action of cycloserine remains for future work, and the resolution of the discrepancy between the sensitivity of animals and man may prove of great eventual scientific value.

Pure, crystalline cycloserine was supplied in capsules, each containing 250 mg. of active antibiotic. The capsules were administered orally in a dose which varied from 1.0 to 1.5 Gm./day, in 4 divided doses. We prefer this spread in the administration because it allows of a more constant blood level[3] and minimizes the fluctuations in tissue fluid levels incident to larger but more infrequent dosing.

Clinical Study

The clinical results with cycloserine in pulmonary tuberculosis are divided into two categories: I) acute, previously untreated cases, and II) chronic, clinically resistant cases.

I) Acute, Previously Untreated Cases

Continuous therapy with cycloserine has now been given for periods up to 10 months (Table I). To date we have had under treatment 25 acute cases: 14 males and 11 females, aged 20 to 60 years. There were five whites, six Negroes, and 14 Puerto Ricans. Data on eight cases, treated up to 16 weeks, were reported previously.[1, 2] In discussing the results, the cases are grouped according to the length of treatment.

Group A—Data on patients after five to nine weeks of treatment. Two of these were hematogenous, another, a miliary infection. The remainder were advanced, cavitary cases, as indicated in Table I.

The 25 patients listed at this early stage of treatment include 12 who were added recently: three on cycloserine alone, and nine on both cyclo-

serine and 300 mg. of INH per day. One was so ill on admission, and so little was known about the effectiveness of cycloserine at that time, that to avoid any possible risk, he was given streptomycin, 1.0 Gm./day for four weeks, thence continued on 1.0 Gm. three times a week, in addition to cycloserine.

Group B—Data on 13 subjects treated for from 12 to 20 weeks. These are the subjects carried over from Group A.

Group C—Data on five subjects who have had continuous therapy with cycloserine for from 32 to 40 weeks. Preliminary data on this group were given previously.[1] Two of the eight subjects left against advice, and one was discontinued because of psychosis which she developed after eight weeks of therapy. A severely diabetic patient with advanced pulmonary tuberculosis received cycloserine for seven months, with satisfactory improvement. Because her sputum was still positive, and her lung lesions were not resolving progressively, INH was added to her regimen. Within seven weeks her sputum became negative on smear and culture.

Results in Acute, Previously Untreated Cases

The data reported in Table I were obtained under the conditions described in the previous publication.[1]

Symptomatic improvement was evident within from three to 21 days in all subjects. There was a gratifying improvement in mental outlook, which was reflected in the desire of the patients to continue treatment.

TABLE I

CYCLOSERINE THERAPY OF PULMONARY TUBERCULOSIS

Data on Acute, Untreated Cases

PRE-TREATMENT DATA

Patients		Age	Sex		Race			Initial Weight	Temperature	Stage of Disease**		X-ray† Appearance		
Groups	No.*	Yrs.	M	F	W	N	PR	Lbs.	Degrees F.	MA	FA	H	CP	FC
Group A	25	32 (20-60)	14	11	5	6	14	116 (82-152)	100.7 (98.6-103.5)	12	13	3	4	18
Group B	13	34 (20-51)	8	5	5	2	6	118 (82-152)	100.3 (98.6-103)	5	8	1	2	10
Group C	5	27 (20-60)	2	3	0	1	4	119 (94-140)	101.4 (100-103.5)	2	3	0	2	3

STATUS UNDER CYCLOSERINE THERAPY

Dose: 20 to 25 mg./Kg./day, orally
X-ray showed "marked" improvement in all cases

Weeks of Therapy	Cycloserine			Weight Gain	Bacillary Content	
	Alone	Combined			Sputum or Gastric Concentrates	
		SM	INH	Lbs.	Smear Neg.	Culture Neg.
5-9	15	1	9	10.5 (0-38)	††18/25	††4
12-20	12	1	0	19 (5-55)	10/13	6
32-40	4	0	1	30 (11-49)	5/5	5

*Group A includes the cases in the groups which follow.
**Classified as far advanced (FA), or moderately advanced (MA), by the criteria listed in Diagnostic Standards, National Tuberculosis Association.
†H = Hematogenous; CP = Caseo-pneumonic; FC = Fibro-cavernous.
††One of these was negative at the start.

1. Reduction of fever occurred in all subjects, in degree depending on the initial extent of the disease. Occasionally at the start of therapy there was a temporary increase in the fever for a few days, followed by a steady, and sometimes precipitous, decrease to normal. In the far advanced, caseous type of pulmonary lesion, the fever was reduced more slowly, up to three weeks being required to reach normal, where it was then maintained. In the case of miliary tuberculosis, previous INH and streptomycin therapy for four weeks had failed to resolve the hyperthermia. Cycloserine given alone reduced the fever within five days, the temperature remaining normal since then.

2. Gain in weight and strength, with rapid amelioration of toxic symptoms, occurred in all patients. Appetite improved promptly, and all but one gained in weight, up to 55 pounds. Some of the patients requested and received additional food. Weight gain progressed with the length of treatment, as shown in Table I.

3. Reduction in cough and sputum occurred shortly after institution of cycloserine, progressively lessening to complete disappearance in most cases.

4. Clearing on x-ray film was marked. The pulmonary lesions, as visualized by serial x-ray films, responded promptly in all of the acute cases. The most marked clearing was noted following the longer treatment, with complete clearing on several occasions (see case history of patient H. V., Figures 1*A* to 1*E*).

5. Bacillary content of the sputum was reduced in all cases. After five to nine weeks of treatment with cycloserine, 17 of 24 subjects who had had positive sputa were now negative on smear, three being negative on culture as well. The 25th subject had miliary tuberculosis, with negative smear at the start. Of the nine receiving both cycloserine and INH, seven are sputum negative on smear, and one on culture.

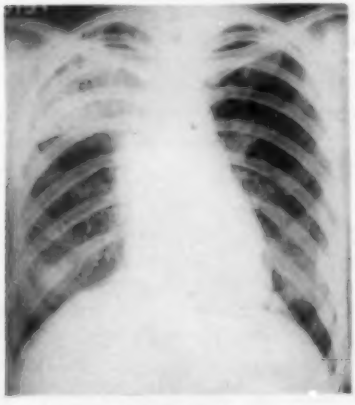


FIGURE 1A

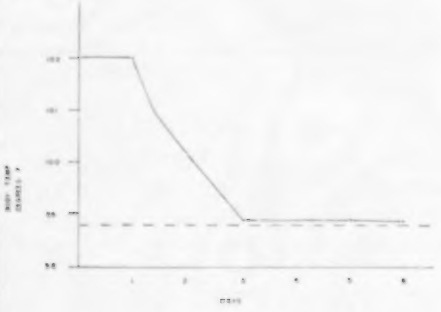
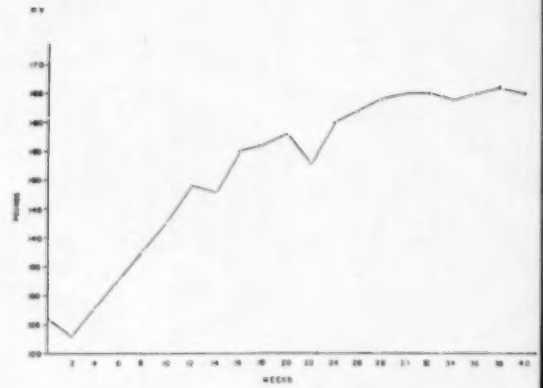
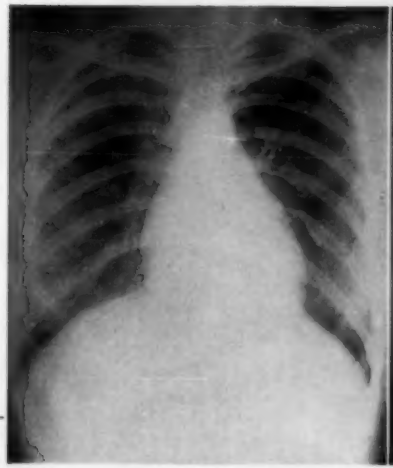


FIGURE 1B

Figure 1A: H. V. Chest x-ray film on admission: caseous pneumonic tuberculous lesion in right upper lobe with cavity.—*Figure 1B:* H. V. Note drop of temperature to normal on third day where it has remained on cycloserine therapy.





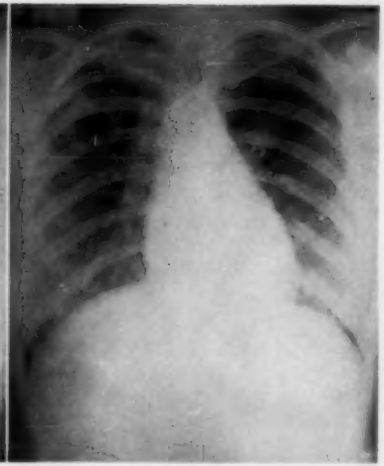


FIGURE 1C FIGURE 1D FIGURE 1E

Figure 1C: H. V. Following a slight initial loss of weight during hemoptysis she has gained weight rapidly and continues to do so.—*Figure 1D:* H. V. X-ray film taken after 12 weeks of cycloserine therapy. Note resolution of inflammatory disease. Cavity can no longer be clearly defined.—*Figure 1E:* H. V. X-ray film after 30 weeks of cycloserine shows complete resolution of the caseous lesions in the right upper lobe; there is a minimal residual productive infiltration.

Thirteen subjects have been treated for from three to five months, at which time 10 were negative on smear and six on culture as well. The three positive sputa are from patients with far advanced, bilateral disease, with multiple cavitation at the start of therapy. However, the sputum of these patients is reduced in amount and contains many less bacilli.

The five who have been on continuous cycloserine therapy for from eight to 10 months have sputa negative for tubercle bacilli on smear and culture. One who left against advice after two months of treatment was negative on smear and culture when discharged. He was readmitted elsewhere, but has remained sputum negative on other therapy. The second who left but returned is also negative. The patient who developed psychosis after eight weeks of treatment was also negative when cycloserine was discontinued, and has remained so on streptomycin and PAS.

The clinical effectiveness of cycloserine on the acute, previously untreated type of pulmonary tuberculosis is well illustrated by the following two case reports:

H. V., a 20 year old Puerto Rican female, was admitted with severe toxemia, temperature of 102° F., hemoptysis, and severe pains in the right chest. There was a history of loss of weight and night sweats of two months' duration. X-ray films taken on admission showed a caseous pneumonic lesion involving the upper one-third of the right lung, with a cavity in the right infraclavicular region (Fig. 1*A*). The sputum showed tubercule bacilli on direct smear (G-II).

Cycloserine therapy was started soon after admission. Response was rapid. The temperature fell to normal by the third day, where it has remained (Fig. 1*B*). Hemoptysis subsided and toxemia disappeared on the fourth day. A slight initial dip in body weight was followed by a steady gain to a total of 40 pounds during the 36 weeks of therapy (Fig. 1*C*). The pneumonic lesion resolved rapidly. The cavity could not be definitely outlined on the x-ray film taken during the 12th week of treatment (Fig. 1*D*). Cough and expectoration were no longer present. Sputum concentrates were reported negative during the fourth week of therapy, and cultures of the sputum and gastric washings have remained negative ever since (15 examinations). The latest x-ray films, including tomographies, fail to disclose cavitation or significant pulmonary pathology (Fig. 1*E*).

P. B., a 28 year old Puerto Rican male, was admitted with a history of productive cough, fever, loss of weight, and fatigue, of three weeks' duration. X-ray films on admission revealed a caseous pneumonic lesion with a cavity in the left mid-lung field (Fig. 2*A*). The sputum contained tubercle bacilli (G-II). Cycloserine therapy was started immediately upon admission. The elevated temperature became normal on the 10th day and has remained so (Fig. 2*B*). His weight rose precipitously to a gain of 55 pounds in 21 weeks (Fig. 2*C*). After eight weeks of cycloserine therapy the sputum became negative on smear and on three subsequent cultures. After 24 weeks, x-ray film discloses slight residual pathology without evidence of cavitation (Fig. 2*D*).

II) Chronic, Clinically Resistant Cases

Each of the 32 patients in this group had active pulmonary tuberculosis of long duration. Preliminary data on 29 of them treated for from eight to 18 weeks were given in a previous report.[1] They had been treated for from one to three years with streptomycin, INH, and PAS in various combinations, but without substantial response. Because they were failures to existing antimicrobial therapy, they were deemed ideal for proof of the effectiveness of cycloserine. At the time of initiation of cycloserine therapy most of these patients were barely holding their own, a few actually retrogressing. Viomycin had been tried in two, along with the other drugs, but without effect. During the 20 to 36 weeks' period of treatment eight receiving cycloserine were discontinued for the following reasons: one, tem-

porarily convulsive; one, epileptic; four, left against advice, and two, because they were unco-operative.

A total of 24 chronic cases are still under cycloserine therapy. At the onset of the study four continued to receive streptomycin and INH along with cycloserine, but these were subsequently discontinued because of absence of apparent advantages over cycloserine alone. There were 19 males and five females, aged 24 to 84 years, of whom 11 were whites, four Negroes, and nine Puerto Ricans.

FIGURE 2A

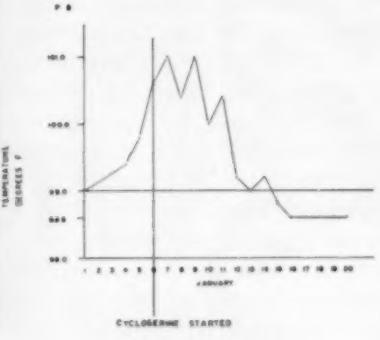


FIGURE 2B

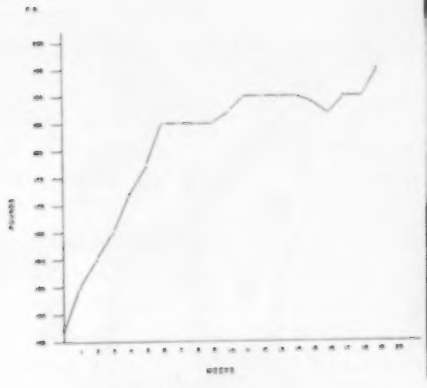


FIGURE 2C

FIGURE 2D

Figure 2A: P. B. Chest x-ray film on admission. Caseous pneumonic tuberculous lesion involving the left mid-lung field with cavity formation.—*Figure 2B:* P. B. Temperature elevated at institution of cycloserine therapy came down to normal during 10 days of treatment, where it has remained.—*Figure 2C:* P. B. Weight increase following onset of cycloserine therapy.—*Figure 2D:* P. B. X-ray film following 24 weeks of cycloserine therapy shows resolution of lesion in left lung with minimal residual productive infiltration.

Results in Chronic, Resistant Cases of Pulmonary Tuberculosis

Symptomatic improvement occurred in all but one case. This patient had improved initially, but lately has been suffering as the result of severe pulmonary fibrosis and emphysema. His appetite remains poor and he has lost slightly in weight. Despite the severity of the tuberculous process in most of these patients, none died under cycloserine therapy, although several would have been expected to do so under previous treatment. Subjects who had a slight recurrent fever before cycloserine were now normal.

1. Gain in weight and strength occurred in most of the subjects a short time after institution of cycloserine therapy. There was evident marked improvement in mental outlook which, together with the fact that patients who had been bedridden for many months soon became ambulatory, created a serious problem on the wards because of the demand for cycloserine by other patients. In 19 there was prompt increase in appetite and gain in weight of from two to 31 pounds (average 11½). Of these, 17 were reported previously.[1] Since that time, 12 of the 17 continued to gain weight, four lost slightly, and one has remained stationary.

Three of the 24 have lost on the average of five pounds since the inception of treatment. One of these had gained initially and then lost; the second had lost two pounds, for a total of eight to date, while the third, who had been stationary has lost three pounds. The two remaining patients are stationary in weight, one since the inception of treatment five weeks previously. The other has lost the three pounds previously gained.

2. Reduction in cough and sputum was marked in all cases, and in most it was difficult to obtain direct sputum for bacteriological and cycloserine levels after four to 10 weeks of treatment. Seven cases only failed to clear completely, but these were markedly atelectatic, bronchiectatic, and cavitary disease cases. It may benefit them to administer cycloserine by aerosol spray, and this is now in progress.

3. Clearing on x-ray film has been marked in five, moderate in 13, and minimal to stationary in six. None showed worsening. Old cavities decreased in size, the fibrotic walls gradually thinning out, making x-ray delineation difficult.

*4. Bacteriological study of the sputum** showed all cases to be strongly positive prior to the initiation of cycloserine therapy.[1] Of the 24 resistant cases on continuous cycloserine therapy, 15 are sputum negative on smear, eight of which have had repeatedly negative cultures as well. The sputum positive cases show less bacteria than previously, and on occasion present a smear-negative specimen.

Of the eight who discontinued treatment, five were negative on smear, with negative culture in two. The other three were persistently positive but were Gaffky reduced.

*This term is used to designate sputum and gastric concentrates, when listed as "negative."

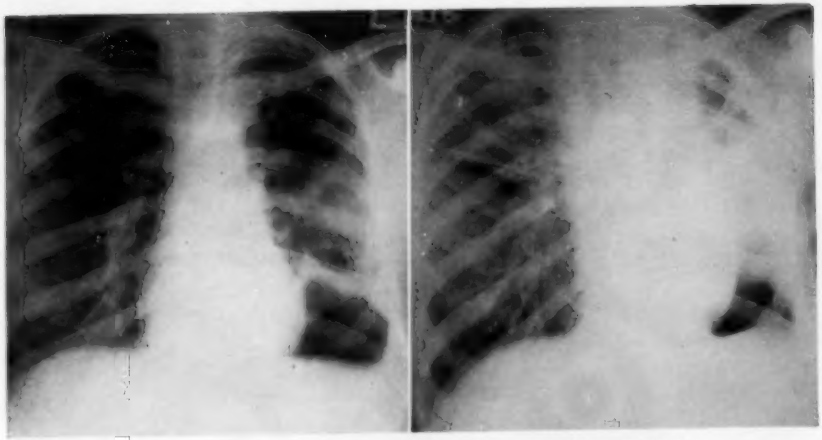


FIGURE 3A

FIGURE 3B

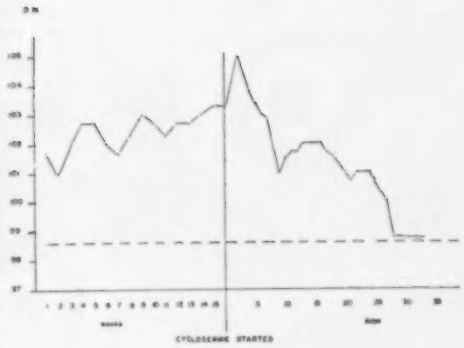


FIGURE 3C

Figure 3A: D. M. Chest x-ray film on admission. Extensive caseous pneumonic tuberculous lesion in lower half of left lung. Left diaphragm paralyzed and elevated because of previous phrenic nerve operation.—*Figure 3B:* D. M. X-ray film at onset of cycloserine therapy shows a marked progression of the disease in the left lung with a large upper lobe cavity. There has also been a spread of the disease into the right upper lobe.—*Figure 3C:* D. M. Temperature that had been elevated for over six months came down to normal within a month and has remained so.

The three described below illustrate the salutary effects of cycloserine on chronic, resistant pulmonary tuberculosis:

D. M. is a 24 year old Puerto Rican male who was admitted in March 1954 with a history of tuberculosis since 1949, previously treated in several hospitals.

He had received courses of streptomycin and PAS at repeated intervals since 1949. In 1952 INH was added along with the previous two drugs, but without response in his pulmonary condition. An x-ray film taken on admission revealed an extensive caseous tuberculous disease in his left lung with paralyzed high left diaphragm, and with evidence of spread of disease to the right lung (Fig. 3A). Due to high fever he was put on viomycin in September 1954, but discontinued 10 weeks later because of the lack of response. Since admission and just prior to cycloserine therapy, he had lost 30 pounds, and was moribund. Figure 3C illustrates the extremely elevated and protracted temperature, despite combined antimicrobial therapy.

An x-ray film taken at this time is shown in Fig. 3B. The entire left lung was involved, with extensive caseous pneumonic tuberculous process. A large cavity occupied the upper third of the left lung. There was evidence of spread and of an increase in the disease of the right upper lobe.

Cycloserine was started orally at a daily dose of 1.5 Gm. A rapid improvement followed. The fever subsided and the temperature became normal within a month of therapy, and has remained so (Fig. 3C). His weight increased rapidly and progressively, as shown in Fig. 3D. Despite the previous gravity of his condition, he is now ambulatory and his sputum is negative on smear for the first time in six years. Cultures are positive occasionally. An x-ray film taken after 12 weeks of cycloserine therapy shows atelectasis of the left lung, absence of the large cavity, and some clearing of the lesion in the right lung (Fig. 3E).

G. D. is a 56 year old Puerto Rican male who was admitted in July 1950, with profuse hemoptysis and history of tuberculosis dating back two years, for which he had received sanatorium treatment. X-ray film on admission showed bilateral cavitary lesions. Figure 4A illustrates his pulmonary disease a year later. Under streptomycin and INH therapy since admission, the pulmonary lesion has remained stationary. The sputum has been consistently positive.

Just prior to cycloserine therapy nine months later, an x-ray film showed the cavity in the right upper lobe to have increased in size. The lesion in the lower lobes remained stationary (Fig. 4B). An immediate increase in appetite accompanied the general improvement. Whereas his weight had been stationary for more than four months, he has since gained seven pounds (Fig. 4C). An x-ray film taken after nine months of cycloserine therapy showed a decrease of shadows of both lungs and a thinning

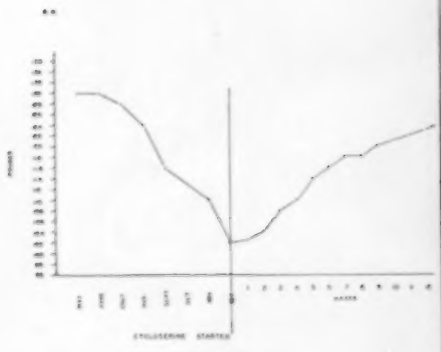


FIGURE 3D

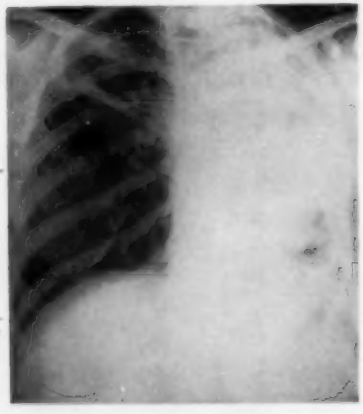


FIGURE 3E

Figure 3D: D. M. His weight which was decreasing steadily since admission rose immediately on institution of cycloserine.—*Figure 3E:* D. M. X-ray film taken after 12 weeks of cycloserine therapy. The left lung has become atelectatic with disappearance of the large left upper lobe cavity. There has been some clearing in the right upper lobe.

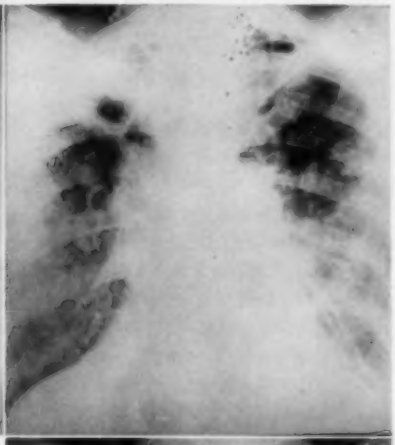
of the cavity wall in the right upper lobe (Fig. 4D). The sputum is now negative on smear and culture, suggesting epithelization of the cavity wall.

J. T. is a 56 year old white male, admitted to the hospital in 1951 with a two year history of cough, expectoration, loss of weight, and night sweats. He had extensive bilateral pulmonary tuberculosis and positive sputum. On streptomycin-INH combined therapy he showed marked clearing of some of the lesions in both lungs. However, the sputum persisted positive for tubercle bacilli. A January 1954 x-ray film revealed cavitary tuberculous disease in the left mid-lung field (Fig. 5A). An x-ray film taken seven months later showed a progression of the disease in the left lung (Fig. 5B).

He was then placed on cycloserine. He gained 10 pounds after having been stationary for more than a year (Fig. 5C). An x-ray film taken after seven months of cycloserine

FIGURE 4A

FIGURE 4B



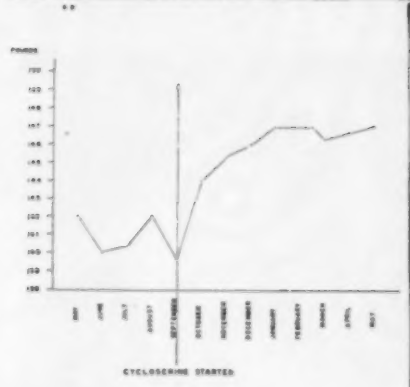


FIGURE 4C

FIGURE 4D

Figure 4A: G. D. Chest x-ray film taken 15 months prior to cycloserine therapy shows bilateral extensive tuberculous disease with a large right apical cavity.—*Figure 4B:* G. D. X-ray film taken at onset of cycloserine therapy. There has been an increase of the size of the cavity in the right upper lobe. The lesion in the lower lobes is stationary.—*Figure 4C:* G. D. His body weight which had been stationary for more than four months began to increase almost immediately after onset of cycloserine.—*Figure 4D:* G. D. X-ray film taken after nine months of cycloserine therapy. There has been a marked decrease of shadows in both lower lobes. The right upper lobe cavity is smaller and its walls are thinned.

showed a complete clearing of the cavitary disease in the left lung (Fig. 5D). Recent tomographic studies fail to reveal cavities. The sputum became negative on smear and culture within four months of treatment, and has remained so.

Toxic Reactions

There has been a low incidence of untoward reactions in the 57 cases of pulmonary tuberculosis thus far treated with cycloserine. The drug has been tolerated well in the daily doses of 1.0 to 1.5 Gm.

Insomnia, dizziness, or sleepiness occurred in four cases within a week of therapy. These symptoms were of short duration and did not recur despite continued treatment. Hyperirritability, increased reflexes, and involuntary tremors were noted in seven male patients. These were not severe and soon disappeared without discontinuing the drug.

Two with previous history of schizophrenia exhibited changes in personality, progressing to outright mental depression during 4 weeks of therapy. A more recent case on combined INH and cycloserine therapy became psychotic after one month. The drug has been discontinued in all of these cases. In the first two mental depression outlasted discontinuance of therapy, throwing doubt on the relationship of the psychosis and treatment. In the third the mental condition improved within two weeks following the cessation of the INH and cycloserine, although he is still under psychiatric observation.

Epileptiform manifestations occurred in two, necessitating discontinuance of therapy. The first was a known epileptic whose control with dilantin was broken after six weeks on cycloserine, despite reduced dosage. She regained her previous state upon cessation of the drug. However, she died of tuberculosis two months later, while under streptomycin-INH treatment.

FIGURE 5A FIGURE 5B

Figure 5A: J. T. Chest x-ray film taken seven months prior to cycloserine therapy reveals a caseous pneumonic lesion in left mid-lung field with cavitation.—*Figure 5B:* J. T. X-ray film taken at the onset of cycloserine therapy. There has been in increase in the severity of the left lung lesion.

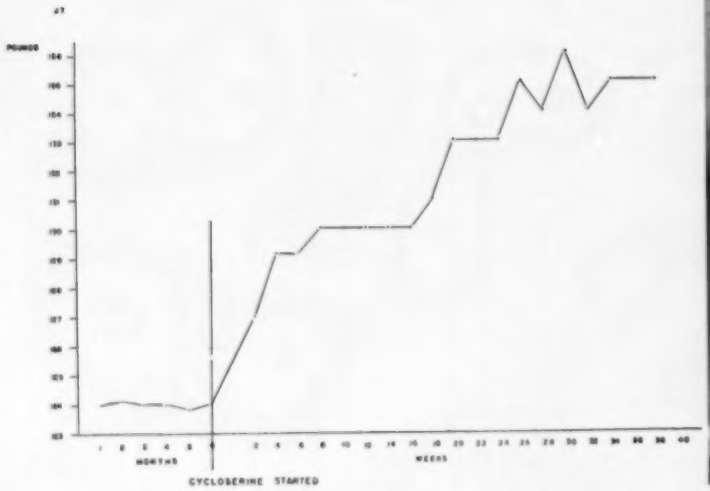


FIGURE 5C

FIGURE 5D

Figure 5C: J. T. Body weight was stationary for over a year prior to cycloserine therapy but rapidly rose on institution of therapy.—*Figure 5D:* J. T. X-ray film taken after seven months of cycloserine therapy. There has been complete resolution of caseous disease and closure of cavities with minimal residual productive infiltration.

The other recovered from the convulsive seizures on discontinuance of cycloserine.

In a previous report[1] we cited the fact that routine examination of the spinal fluid of 30 patients showed an increase in protein concentration in eight. This was slight and yet, because of the neurological symptoms listed above, we have examined other patients, and re-examined those who had shown this abnormality. Finding protein increase has not been confirmed, and because no other changes were present suggesting central nervous system toxicity its significance remains in doubt.

Three patients developed skin rashes during prolonged administration of cycloserine. They cleared upon interruption of treatment and administration of antihistaminics. One of these recurred upon resumption of cycloserine. This patient was a nervous individual, with evidence of having nonspecific neurodermatitis incidental to cycloserine or perhaps exaggerated by it. She insisted upon continuing cycloserine because of the improvement in her pulmonary condition, and has not shown any further ill effects, while the rash is slowly fading.

There have been no blood, urinary, or ECG changes. Liver and kidney function tests have been consistently negative in all cases. Blood plasma and tissue fluid concentrations of cycloserine have been determined on many and these data are being made the subject of another report.

No resistance of the tubercle bacilli to cycloserine was encountered *in vitro*[7] or clinically thus far, during the 10 months of our study. This is in contrast to streptomycin and INH, to which bacterial resistance develops rapidly.

SUMMARY AND CONCLUSIONS

Cycloserine, a new antibiotic, has been used in the treatment of 57 cases of pulmonary tuberculosis. These include the 37 original cases previously reported[1] and 20 additional subjects. Twenty-five were acute cases, previously untreated; 32 were chronic cases, therapeutically resistant to prior antimicrobial therapy.

Cycloserine was administered orally in a dose of 20 to 25 mg./Kg. of body weight per day (1.0 and 1.5 Gm.), in divided doses.

The incidence of side reactions was low. On the basis of neurological symptoms, both excitatory and depressant, it was necessary to discontinue therapy on five patients. Skin rashes of short duration and unknown cause occurred in three, in all of whom cycloserine was continued without further difficulty.

Although this study has run for a comparatively short time (five to 40 weeks), the following conclusions may be drawn from the data at hand:

1. Cycloserine has been found to be an efficient antibiotic agent in the treatment of acute, previously untreated cases of pulmonary tuberculosis. Sputum conversion, x-ray film clearing, gain in weight, and reduction of fever occurred promptly.

2. It fills the need for an antimicrobial agent in those cases of chronic tuberculosis which have failed to respond to existing drugs, especially patients who are inoperable because of extent of disease or poor condition.

3. In the daily dose of 20 to 25 mg./Kg. of body weight, over periods of up to 10 months of continuous therapy, cycloserine elicited few reactions other than those on psychotics and epileptics. The milder untoward symptoms disappear upon continued therapy.

4. Resistance to cycloserine by the tubercle bacillus has not developed either clinically or in *in vitro* studies. This is in contrast to presently available antitubercular drugs.

5. Studies are being carried out to determine the therapeutic compatibility between cycloserine and streptomycin, or INH. There may result a mixture between these which will prevent resistance and diminish or abolish toxicity.

Acknowledgements: We are indebted to Michael G. Mulinos, M.D., Medical Director of Commercial Solvents Corporation, for supplies of cycloserine and for the valuable help and advice that he has rendered throughout this investigation. For sputum cultures and resistance studies we are indebted to Lois Lillick, M.D., Professor of Bacteriology—for cycloserine concentrations in various tissue fluids, to Harry Baron, Ph.D., of the Department of Biochemistry, New York Medical College.

RESUMEN Y CONCLUSIONES

Se ha usado la cicloserina, un nuevo antibiótico, en el tratamiento de 57 casos de tuberculosis pulmonar. Estos incluyen los 37 casos originales previamente reportados más 20 adicionales. Veinticinco eran casos agudos sin tratamiento previo; 32 eran casos crónicos, terapéuticamente resistentes a la terapia antimicrobiana anterior.

La cicloserina se administró oralmente en dosis de 20 a 25 mg./kg. de peso corporal diariamente (1.0 y 1.5 Gms.) en dosis divididas.

La frecuencia de reacciones colaterales fué baja. Fué necesario interrumpir la terapia en cinco de los pacientes debido a la presencia de síntomas neurológicos tanto excitatorios como depresivos. Se presentaron eritemas de corta duración y de causa desconocida en tres, en to dos los cuales se continúa la administración de cicloserina sin dificultades posteriores.

A pesar de que este estudio se ha llevado en relativamente pocotiempo (cinco a cuarenta semanas), se pueden sacar las siguientes conclusiones de los datos a la mano:

1. Se encontró que la cicloserina es un agente antibiótico eficaz en el tratamiento de los casos agudos de tuberculosis pulmonar no tratados previamente. Se obtuvo rápidamente la conversión del esputo, la limpieza de las películas radiográficas, aumento de peso y reducción de la fiebre.

2. Llena los requerimientos de un agente microbiano en los casos de tuberculosis crónica que no han respondido a las drogas ya existentes, especialmente en pacientes inoperables debido a lo avanzado de su enfermedad o a sus malas condiciones.

3. En las dosis diarias de 20 a 25 mg./Kg. de peso corporal, por períodos de hasta 10 meses de terapia contínua, la cicloserina no despertó otras reacciones que las de psicosis y epilepsia. Los síntomas menos graves de aparición posterior desaparecen al continuar la terapia.

4. No se ha desarrollado resistencia del bacilo a la cicloserina ni en los estudios clínicos ni en los in vitro. Esto contrasta con las drogas antituberculosas con que se cuenta.

5. Se están llevando a cabo estudios para determinar la compatibilidad terapéutica entre la cicloserina y la estreptomicina o INAH. Puede resultar una mezcla entre ellas que provenga a resistencia y disminuya o suprima la toxicidad.

RESUME

Un nouvel antibiotique, la cyclosérine, a été utilisée dans le traitement de 57 cas de tuberculose pulmonaire Ceux-ci comprennent les 37 cas précédemment rapportés. 22 d'entre eux étaient des cas aigus, et non traités auparavant. 32 étaient des cas chroniques, résistants à une première thérapeutique antimicrobienne.

La cyclosérine fut administrée par la bouche, à la dose de 20 à 25 mmgr. par kilogramme de poids corporel chaque jour (1 à 1,5 gr. en doses fractionnées).

La fréquence des réactions secondaires fut peu importante. Par suite de symptômes neurologiques à la fois excitants et dépressifs, il fut nécessaire de cesser le traitement chez cinq malades. Des éruptions cutanées de courte durée de cause inconnue, survinrent chez trois malades; chez tous les autres la cyclosérine fut continuée sans aucune difficulté ultérieure.

Bien que cette étude porte sur un temps de comparaison court (5 à 40 semaines) les conclusions suivantes peuvent être tirées des constatations:

1. Les auteurs ont trouvé que la cyclosérine est un antibiotique efficace dans le traitement des cas aigus de tuberculose pulmonaire non traitée auparavant. La négativation des crachats, le nettoyage radiologique, l'augmentation de poids et la réduction de la fièvre surviennent rapidement.

2. Elle offre un nouvel agent antimicrobien dans les cas de tuberculose chronique qui ont résisté aux médications existantes, en particulièr chez les malades que l'extension de a maladie ou un mauvais était général rendent inopérables.

3. Aux doses quotidiennes de 20 à 25 mmgr. par kilogramme de poids corporel, pendant des périodes allant jusqu'à 10 mois de traitement ininterrompu, la cyclosérine n'a occasionné que peu de réactions secondaires, sauf chez les psychopathes et les épileptiques. Les réactions secondaires plus discrètes finissent par disparaitre après traitement continu.

4. La résistance du bacille tuberculeux à la cyclosérine ne s'est pas constituéée soit cliniquement, soit dans les recherches *in vitro*. Ceci s'oppose à ce que nous connaissons à l'heure actuelle des médications antituberculeuses.

5. Des études sont poursuivies pour déterminer la compatibilité de la cyclosérine et de la streptomycine ou de l'isoniazide. Il se peut qu'une combinaison entre les produits empêche la résistance et diminue ou supprime la toxicité.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Cycloserin, eine neue antibiotische Substanz wurde bei 57 Patienten mit Lungentuberkulose angewandt. Darin sind die 37 Patienten, über die schon früher berichtet wurde, eingeschlossen. Bei 25 Patienten lag eine akute Erkrankung vor: eine frühere Therapie hatte nicht stattgefunden;

32 Fälle waren chronische Tuberkulosen, die gegenüber früherer Chemotherapie resistent waren.

Cycloserin wurde per os in Dosen von 20 mg-25 mg/kg Körper gewicht (1,0-1,5 g pro die) in mehreren Einzelgaben verabreicht.

Nebenerscheinungen traten selten auf. Wegen des Auftretens neurologischer Symptome (Erregung oder Depression) musste die Therapie bei 5 Patienten unterbrochen werden. Hautausschläge von kurzer Dauer und unbekannter Ursache traten bei 3 Patienten auf: das Cycloserin konnte jedoch ohne Schwierigkeiten weiter gegeben werden.

Obgleich diese Untersuchungen nur verhältnismässig kurze Zeit liefen (ca. 5 bis 40 Wochen), sollen die folgenden Schlüsse an Hand der zur Verfügung stehenden Daten wiedergegeben werden:

1. Im Cycloserin liegt eine wirksame antibiotische Substanz für die akute, nicht vorbehandelte Lungentuberkulose vor. Sputumkonversion, röntgenologische Besserung, Gewichtszunahme und Fieberrückgang traten schnell ein.

2. Es erfüllt die Voraussetzungen für eine antimikrobielle Substanz in solchen Fällen der chronischen Lungentuberkulose, die auf die bisher bekannten Tuberkulostatika nicht angesprochen hatten, besonders bei Patienten, die wegen der Ausdehnung des Prozesses oder des schlechten Allgemeinzustandes inoperabel waren.

3. Bei einer täglichen Dosierung von 20 mg-25 mg/kg Körpergewicht während ununterbrochener Medikation bis zu zehn Monaten verursachte das Cycloserin nur wenige Nebenerscheinungen bei Kranken mit Psychosen und Epilepsie. Leichtere Nebenerscheinungen verschwinden im Laufe der weiteren Behandlung.

4. Resistenz gegenüber Cycloserin konnte weder klinisch noch bei der bakteriellen Kultur der Tuberkulose gefunden werden. Dieses steht in Gegensatz zu den Ergebnissen bei den bisher verwandten Tuberkulostatika.

5. Untersuchungen zur Bestimmung der therapeutischen Verträglichkeit von Cycloserin und Streptomycin oder Isoniazid laufen noch. Möglicherweise lässt sich eine Kombination aus diesen Tuberkulostatika herstellen, welche die Resistenz verhindert und sehr wenig oder gar nicht toxisch ist.

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Cor Pulmonale: Its Diagnosis and Management

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The diagnosis of cor pulmonale, heart disease secondary to lung disease, calls for close cooperation between the chest physician and the cardiologist. Inasmuch as the cardiac involvement is rooted in the underlying pulmonary dysfunction, therapy—if it is to be successful—must be directed at both pulmonary and cardiac aspects of the disease. I shall go even further and say that treatment of the cardio-circulatory complications will be successful only insofar as the nature and extent of the pulmonary disease is known and its consequences fully appreciated.

I should like to make a distinction at this point between "primary" cor pulmonale (disease of the right side of the heart in which pulmonary hypertension is the basic lesion), and "secondary" cor pulmonale, in which the basic lesion lies not in the pulmonary circuit but beyond, in the left side of the heart. The damming back of blood into the pulmonary circulation because of obstructive lesions in the left side of the heart—mitral stenosis, constrictive pericarditis resembling mitral stenosis in its effects, or tumor of the atrium, to mention but a few—may produce congestion of the pulmonary capillaries which, if not corrected, may progress into pulmonary edema and hypoventilation of the air sacs, thus heightening pulmonary arterial tension and affecting the right side of the heart. In this paper, I am not concerned with such "secondary" cor pulmonale, which must be attacked by correcting a co-existing lesion in the left side of the heart. Let me mention, however, that by far the most common diagnostic error made in patients with chronic bronchitis and emphysema with heart failure is to overlook associated heart disease due to other causes. Because of the nature of cor pulmonale, the murmur of a valvular lesion may be obscured, and the possibility of ischemic heart disease may be difficult to exclude.

Detection of Pulmonary Hypertension

In the patient with obvious failure of the right side of the heart—in whom edema, distended neck veins, ascites, hepatomegaly and cyanosis are present—the diagnosis of cor pulmonale is made without hesitation. However, enlargement of the right ventricle is often a late sign in patients with cor pulmonale: In the absence of heart failure the heart size is likely to be normal; even if present, enlargement of the various cardiac chambers cannot be determined by physical examination in the patient with severe chronic pulmonary disease. The presence of an accentuated pulmonary second sound and a forceful subxiphoid pulse should be viewed with suspicion.[1] Probably the most important clinical symptom of pulmonary hyper-

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tension is fatigability; the most characteristic symptom of heart failure, dyspnea.

X-ray evidence: The heart borders may appear quite normal in posterio-anterior view, for with enlargement of the right side of the heart, the heart may rotate. However, *lateral* and *oblique* views of the heart may reveal definite enlargement of the right ventricle, the right auricle, and the pulmonary artery segment. Enlargement of the pulmonary arc frequently is the first indication of cardiac hypertrophy. Other roentgenographic evidence of increased pulmonary arterial pressure includes: (1) growing prominence of pulmonary arteries as demonstrated in serial studies; (2) dilatation and pulsation of the pulmonary arteries under increased arterial pressure; and (3) displacement of air within the air sacs by lymph stasis or edema.[2] Serial roentgenographic examinations over a period of months or years are most helpful in mapping the progress of the disease.

Electrocardiographic evidence: The electrocardiogram may show signs of right ventricular hypertrophy before the enlargement is apparent on x-ray examination. Characteristic findings consist of high R-waves in leads over the right precordium and deep S-waves in leads over the left precordium. Depression of the ST-interval and T-wave inversions over the right side of the heart are also of diagnostic value.[3]

Vectorcardiography often is most helpful in determining early degrees of right ventricular hypertrophy.

Evidence from cardiac catheterization: Although cardiac catheterization is the only method whereby pulmonary hypertension can be accurately assessed, clinical, x-ray and electrocardiographic evidence strongly suggestive of the presence of pulmonary hypertension, as heretofore described, make confirmatory catheterization studies unnecessary in most instances. Cardiac catheterization should not be employed in the older, cyanotic patient, where it may prove dangerous and may actuate respiratory acidosis.

Downhill Course of Disease

Fulton[3] has described three stages in the down-hill course of the disease process: In the first stage, which may last from fifteen to twenty years, the patient complains only of cough and sputum. This period Fulton calls the stage of "good exercise-tolerance."

During the second stage—over a period of two to five years—there is a progressive limitation of activity. Usually the second stage is insidious in origin, but it may have begun abruptly after a severe chest infection. The patient fails to note striking alterations in exercise-tolerance from day to day; yet his capacity for effort diminishes steadily, and he is forced to lay off work for increasing periods each winter. At this time the anteroposterior diameter of the chest is found to have increased, with a slight to moderate non-angular kyphosis present. Chest expansion during this stage never exceeds 1½ inches. Cardiac dullness is decreased or absent, and the apex beat is difficult to localize.

Last comes the terminal stage, during which the patient is almost

totally disabled. Peripheral edema first becomes apparent at this time in most instances, although many older patients with chronic pulmonary disorders have edema of the ankles long before signs of right heart failure make their appearance. In these older patients, ankle edema results from decreased cardiac output with subsequent salt and water retention rather than from increased venous pressure secondary to right heart failure. During the terminal stage, in addition to cough, sputum and dyspnea on exertion, weight loss is common. Regrettably, the clinician often sees patients for the first time after the disease is far advanced and little more than palliative measures can be attempted.

Chronic cor pulmonale is much more frequently observed at necropsy than the clinical diagnosis would indicate. Waltzer and Frost[1] discuss 54 patients who received a pathologic diagnosis of cor pulmonale: the clinical diagnosis had been made in only 21, 13 of whom were in cardiac failure before death.

Etiology of the Pulmonary Hypertension

Fortunately, the lungs have capacity for the exchange of gases which is twenty times that required for adequate ventilation while at rest. Because of this excess capacity, marked impairment of the lungs with consequent involvement of the pulmonary vasculature may exist without evidence of strain on the right side of the heart. Nevertheless, any condition which alters to any great extent the normal respiration may influence the lesser circulation and, in turn, the right side of the heart, which has not the power to withstand sudden or long continued strain or increased arterial pressure. Sudden interference with the function of the pulmonary vasculature causes development of acute dilatation, followed by sudden death. More gradual restriction results in chronic cor pulmonale. Acute infections of the lungs, too, may impede pulmonary circulation and produce strain of the right side of the heart.

Forms of pulmonary disease which most commonly compromise the circulation and result in cor pulmonale are chronic obstructive pulmonary emphysema, any of the various types of pulmonary fibrosis, and granulomatous lesions which tend to result in fibrosis. Other conditions commonly associated with enlargement of the right side of the heart—with or without heart failure—include thrombi of either pulmonary arteries or of the nutrient arteries going to the bronchi, disseminated bronchial carcinoma, tuberculosis, bacterial pneumonia, severe kyphoscoliosis (in which the circulatory complications may be related to the accompanying emphysema), asthma and bronchiectasis, atheromatous plaques, and intimal and medial thickening of vessels of different calibers. Chronic anoxia may cause engorgement of the circulation through increases in blood volume, also contributing to the pulmonary hypertension. Intrinsic disease of the bronchial airways and loss of the elastic support of the arterioles frequently occur together and accentuate the obstruction to air flow.

Abnormalities of the chest cage and various neuromuscular and musculoskeletal disorders may also lead to alveolar hypoventilation: deformities of the chest, kyphosis of the thoracic spine, funnel chest and other

anomalies of the thoracic cage may tax the pulmonary circulation severely and often cause cardiac distress through increased strain on the right side of the heart. Obesity interferes in two ways with the pulmonary circulation: first, in the manner of chest deformities, by displacing and confining the viscera of the chest and, second, through interference with proper diaphragmatic action. Westermark[4] has shown that roughly one-third of the vital capacity comes from expansion of the thorax and two-thirds results from descent of the diaphragm. Abdominal tumors, enlargement of the liver, and adhesions to the diaphragm from any cause may prevent full diaphragmatic excursion, with resulting hypoventilation of adjacent lung bases.

Management of Right Heart Failure

Once the factor or factors responsible for the pulmonary hypertension have been determined, treatment can begin. Obviously, therapy outlined for the patient with pulmonary emphysema will differ from therapy outlined for the patient with pulmonary fibrosis; and, again, therapy directed at control of disseminated pulmonary carcinoma, for example, will differ widely from therapy in either of the other diseases. In all three instances, nevertheless, management of failure of the right side of the heart will follow a single pattern: *Rest*, of course, is a primary requisite. *Digitalis* is, to my way of thinking, as important in treating failure of the right side of the heart as in treating failure of the left side. My preferences are Ouabain,® Cedilanid,® and fast acting glycosides such as Gitalin.® Although some clinicians, DeGraff[5] among them, counsel slow, stepwise administration of increasing doses of digitalis in order to prevent increase in pulmonary arterial pressure, I have never found this necessary. It is my practice to start the patient at or near the optimal dose. *Excess weight* is reduced to normal. Excess body fluids are attacked through the use of *mercurial diuretics*—either intramuscularly or orally—and *salt restriction*. *Carbonic anhydraze inhibitor* (Diamox®) is used to augment the diuretic effect of the mercurials and for its respiratory effect. Alleviation of the heart failure also benefits respiration as it lightens the hypoxia.

Management of Emphysema
Relationship to Right Heart Strain and Failure

Chronic pulmonary emphysema, which is the most common cause of pulmonary hypertension, disturbs pulmonary function through impeding air flow in and out of the lungs; results in uneven distribution of air in the alveoli, and causes blood returning to the lungs to be similarly unevenly distributed to the alveoli. Vaporized bronchodilators usually are effective in relieving simple ventilatory insufficiency resulting from bronchiolar spasm and mucosal edema, when used either in a manual nebulizer or, better still, in a nebulizer employed in conjunction with a positive pressure apparatus. Bothersome secretions and exudates often treat at once the "trivial respiratory infections" which may precipitate can be ended by the use of antibiotics. Most important, watch for any severe pulmonary insufficiency, for these patients cannot tolerate even

a small encroachment upon their very limited pulmonary reserve: In persons with advanced emphysema, respiratory infections have a suffocating effect, causing severe hypoxia and hypercapnia which, if prolonged, may give rise to failure of the right side of the heart, cerebral depression, coma, and even death.[6] Response to antibiotics is often dramatic: the patient's general condition improves rapidly, and edema disappears in a few days without other therapy.

The Problem of Respiratory Acidosis

Respiratory acidosis is the biochemical expression of alveolar hypoventilation; its presence is indicated by an elevation of the PCO_2 of the arterial blood. Breathing of carbon dioxide has been employed in various circumstances to stimulate respiration, clear air sacs of lymph, relieve anoxia and lessen tension within the pulmonary capillaries, thus reducing strain on the right side of the heart. If, however, an important lesion already handicaps the left auricle or ventricle, too rapid breathing may result in an over-rapid delivery of blood to an already overloaded left auricle and ventricle, further embarrassing heart action.

Acute respiratory acidosis should be suspected if broncho-pneumonia, severe bronchitis, asthma or acute heart failure develop in the patient. Relative immobility of the chest, tachypnea, retraction of the intercostal spaces, marked diminution of breath sounds, inability to raise secretions and cyanosis also indicate possible development of the syndrome.[7] Like signs and symptoms are present in emphysematous patients with *chronic respiratory acidosis*, but, for the most part, are long standing and unrelated to the current acute episode. Ordinarily, dyspnea is less pronounced in the patient with chronic respiratory acidosis for similar degrees of alveolar ventilation adequacy. Because of the frequent association of cor pulmonale and chronic respiratory acidosis, the onset of right heart failure should alert the clinician to the likelihood that respiratory acidosis may also be present. Polycythemia, too, should suggest the presence of chronic respiratory acidosis.

Treatment of Respiratory Acidosis

Oxygen: If CO_2 retention and narcosis are present as well as oxygen want, respiratory response to carbon dioxide is known to be diminished, and hypoxia is the primary stimulus to breathing. Administration of oxygen leads to a lessening of the cyanosis and improves arterial oxygen saturation but results in *decreased ventilation* because of the elimination of the hypoxic stimulus to respiration. As a result, drowsiness and even coma are frequently seen as consequences of oxygen administration. However, oxygen must be administered if hypoxia is very severe (arterial oxygen saturation of below 85 per cent). Provided only a moderate increase in oxygen content of the inspired air is permitted; bronchodilator therapy is used in conjunction with the oxygen administration; and the patient is removed from the elevated-oxygen atmosphere each hour for as long a period as he can tolerate, it may be possible to improve oxygen-

ation without increasing arterial PCO_2. Or, we may decide to give 100 per cent oxygen through an intermittent positive pressure face mask, which can be done without a decrease in ventilation. Again, oxygen may be given with the use of a mechanical respirator, which will permit administration of oxygen without diminution in ventilation.

Bronchodilators: We prefer the use of Isoprel® 1:200, which may be administered either by aerosol nebulizer or with oxygen under pressure. In the occasional patient whose airways are so obstructed that inhaled bronchodilator is ineffective, aminophyllin may be administered either by rectum or intravenously.

Detergents: Alevaire® and similar detergents tend to liquefy sticky secretions and make them easier for the patient to bring up.

Antibiotics: Because inflammatory swelling of the bronchiolar mucosa contributes to the obstructive process, adequate antibiotic administration is important in providing a sufficient airway.

Helium and oxygen: A mixture of 80 per cent helium and 20 per cent oxygen finds freer passage through narrowed airways than either room air or oxygen. Nevertheless, because the oxygen concentration is no higher than in the room air, this helium and oxygen mixture is no substitute for oxygen therapy in severely hypoxic patients.

Sedation: Sedation is kept to a minimum in order to avoid further depression of the respiratory center.

Pneumoperitoneum: Pneumoperitoneum results in markedly increased mobility of the diaphragm and in a decided increase in vital capacity in emphysema, tuberculosis involving the bases of the lungs, and various other lung disorders.[8, 9, 10]

Diaphragmatic breathing training: Clinically it is apparent that effective diaphragmatic training usually results not only in simple improvement of ventilation but also in more effective cough mechanism with improved evacuation of bronchial secretions. Better control of the almost inevitably recurrent bronchial infections is achieved thereby. Experience with this method of treatment indicates that in patients with less severe disease, diligent continuation of this training frequently will produce striking recovery of function.[11]

Abdominal belt: If the abdominal muscles have been weakened by age or illness and have lost their tone and contractile power, support of the abdomen by an abdominal belt increases diaphragmatic action and improves filling of the right side of the heart.

Cortisone and ACTH: As a general rule, neither cortisone nor ACTH should be given patients with heart disease because of the resultant retention of sodium.

Complicating Factors in Emphysema

The following findings should suggest the presence of some disorder in addition to pulmonary emphysema with cardiac involvement: (after Fulton[3])

Cardiac pain.

Paroxysmal nocturnal dyspnea.
Sudden increase in dyspnea, except when it follows closely on acute respiratory infection.
Clinically apparent cardiac enlargement.
Sustained auricular fibrillation.
Abnormal left axis deviation, or left bundle branch block.
An age over 65 years (more probably due to degenerative heart disease).
Obesity.

SUMMARY

Clinicians are faced with three problems in the diagnosis and management of cardiac disease secondary to pulmonary dysfunction: first, the detection of clinical symptoms of pulmonary hypertension: second, the determination of the particular condition or conditions responsible for the hypertension, and the correction of these conditions insofar as possible; and third, the management of the cardiac symptoms. May I stress again the importance of determining the primary cause of the pulmonary hypertension before any treatment is undertaken?

RESUMEN

Los clínicos tienen que hacer frente a tres problemas en el diagnóstico y el tratamiento de la enfermedad cardiaca consecutiva a una disfunción pulmonar: Primero, el descubrimiento de los síntomas clínicos de la hipertensión pulmonar; segundo, determinación de afección o afecciones causantes de esa hipertensión y la corrección de esas afecciones en lo posible; y tercero, el tratamiento de los síntomas cardiacos. Puedo otra vez recalcar la importancia de determinar la causa primaria de la hipertensión pulmonar antes de emprender cualquier tratamiento?

RESUME

Dans le diagnostic et le traitement d'une affection cardiaque secondaire à la perturbation de la fonction pulmonaire, le médecin se trouve devant trois problèmes:

1. La mise en évidence des symptômes cliniques d'hypertension pulmonaire.
2. La détermination de la condition particulière ou des conditions responsables de cette hypertension et leur traitement dans la mesure du possible.
3. Le traitement des symptômes cardiaques. L'auteur insiste de nouveau sur l'importance qu'il y a à déterminer la cause première de l'hypertension pulmonaire avant que tout traitement soit entrepris.

ZUSAMMENFASSUNG

Der Kliniker sieht sich bei der Diagnose und Behandlung von sekundären Herzkrankheiten nach respiratorischer Dysfunktion drei Problemen gegenüber:

1. der Aufdeckung klinischer Symptome einer pulmonalen Hypertonie,
2. der Erkennung der besonderen Bedingung oder Bedingungen, die für diese Hypertonie verantwortlich sind und Abänderung dieser Be-

dingungen soweit möglich,

3. der Behandlung der kardialen Symptome.

Darf ich nochmals auf die Wichtigkeit hinweisen, zunächst die primäre Ursache der pulmonalen Hypertonie zu ermitteln, ehe eine Behandlung unternommen wird?

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The Handling of the Poor Risk Patient with Pulmonary Tuberculosis: Antimicrobial Therapy, Cardio-Pulmonary Function and Surgery*

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I. Introduction

The remarkable development of antimicrobial therapy for pulmonary tuberculosis, either as the sole modality of treatment or in preparing and covering the patient who is to undergo surgery, has resulted in alteration of our concepts of the treatment of this disease. The prompt clearing of the inflammatory process of the more acute forms, under the influence of antimicrobial agents combined with surgical extirpation of fibrocavernous residua, has resulted in a shortened period of hospitalization.

The so-called "salvage" case is a challenge to the profession both in the evaluation and the employment of refined methods of treatment. Today, we are reluctant to settle for the so-called "good chronic" with quiescent disease. Instead, we are constantly striving for the inactive state.[1]

In this communication, we propose to discuss the "team concept" of management and the ever-broadening horizons for the patient with far advanced pulmonary tuberculosis.

II Pathogenicity of the Tubercle Bacillus and Present Protocols of Treatment

More recently, observations in our laboratory involving the changed metabolism and pathogenicity of isoniazid-resistant tubercle bacilli have led us to formulate new protocols of antimicrobial therapy,[2] particularly in regard to broadening the indications for surgery.

At the National Jewish Hospital, we use essentially three protocols of treatment: (1) Isoniazid as the sole agent which is started initially at eight mgm. or more/kilo/day dose level (with pyridoxine). This protocol is used only for the patient who has had streptomycin and/or PAS treatment before admission and whose organisms in sputum and body fluids are resistant to one or both of these drugs or when previous streptomycin was of sufficient duration and toxicity to justify single drug treatment. (2) A combination of streptomycin, one gram every third day, and isoniazid, eight mgm. or more/kilo/day (with pyridoxine). Both of these drugs are continued until two consecutive negative sputa (concentrate and culture) are obtained. When this goal is achieved, isoniazid is often decreased to four mgm./kilo/day. Streptomycin is discontinued at the

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end of six to 12 months; however, isoniazid is continued for no less than 18 months. If reversal of infectiousness is not obtained, we continue with isoniazid indefinitely. When bacterial resistance to isoniazid at 10 mcg./ml. of medium occurs and the tubercle bacilli isolated give a negative catalase reaction,[2] isoniazid is continued alone but often at a four mgm./kilo/day dose. The criteria for selection for this protocol are as follows: (a) The patient who has had isoniazid and/or streptomycin and/or PAS before coming to the hospital. (b) The absence of obvious cavitation. (c) When organisms are still streptomycin sensitive. If the patient is scheduled for surgery, pre-operatively, he is given streptomycin, one gram every day, and PAS, 12 grams daily, for seven days; this regimen is continued for six weeks post-operatively and then reversed to the established protocol. (3) The third protocol is used for the fresh case of pulmonary tuberculosis who has had no antimicrobial drugs and whose tubercle bacilli are sensitive to them. This regimen consists of streptomycin, 25 mgm./kilo/day for 90 days; then streptomycin is discontinued. Isoniazid is started in an eight mgm. or more/kilo/day dosage (with pyridoxine) with the streptomycin, and the former is decreased to four mgm./kilo/day only if and when two consecutive negative sputa (concentrate and culture) are obtained; or if complete bacterial resistance to isoniazid and catalase negativity develop. It should be noted that in all the protocols, isoniazid is continued for at least 18 months. To obviate the problem of peripheral neuritis we also add thiamine hydrochloride, 100 mgm./day, and, most importantly, pyridoxine, 25-100 mgm./day.[3] In this regimen we utilize the known bactericidal synergism of streptomycin and isoniazid as well as taking advantage of the information collected from clinical observations when streptomycin was the only effective antimicrobial agent available and rapid clearing of the lesions occurred on large doses of streptomycin before bacterial resistance developed.

There is a school of thought which feels that the two most potent antimicrobial agents should not be used together in a new case.[4] However, we believe, the most effective combination of drugs is streptomycin *in adequate dosage* combined with isoniazid. It is also our belief that bacterial resistance to isoniazid is different in its clinical significance from bacterial resistance to streptomycin. We, and others,[5, 6] have observed that catalase-deficient tubercle bacilli (resistant to isoniazid) are moderately or markedly attenuated for the guinea pig, rabbit, monkey and probably for most human beings. We have no evidence of progressive extension of tuberculous disease into previously uninvolved areas of the lungs, or elsewhere, in patients on adequate dosage of isoniazid—even in the face of complete bacterial resistance to this drug. It has been noted that in most cases where the patient is on both isoniazid and streptomycin and develops isoniazid-resistance, streptomycin sensitivity is usually maintained. In attempting to explain this phenomenon, it has been shown that DNA (desoxyribonucleic acid) inactivates streptomycin by simple acid base binding.[7] It has been demonstrated that the DNA is present in open cavities where autolysis of leukocytes is taking place. This may well

account for the prolonged streptomycin susceptibility of the tubercle bacilli appearing in the sputum. Therefore, we continue to use streptomycin and isoniazid under these circumstances because some streptomycin may become therapeutically available, especially in higher and daily doses. When using large doses of streptomycin and isoniazid simultaneously, we have occasionally seen rapid sterilization of cavities which remained as open, cystic structures.[7] Indeed, the pathologist oftimes can no longer unequivocally state that the cavity is tuberculous. It must be recognized that the antimicrobial agents are active only against multiplying (living) organisms. This fact serves as a theoretical basis for our practice of long-term chemotherapy with isoniazid and for our abandonment of long-term rest.

III. Pulmonary Function Determination and Evaluation

Patients with pulmonary tuberculosis are poor risks for surgery not only because of their tuberculous lesions (except in rapid fulminating and toxic phases of this disease) but rather because of respiratory deficiency.[8, 9]

Pulmonary function studies, therefore, assume an even greater importance in evaluating the poor risk patient and fall into two large categories: (a) ventilatory function and (b) interchanges of gases. For practical purposes, the ventilatory function determinations perhaps are of most clinical significance. However, oxygen saturation and perfusion, and shunt determinations are important and occasionally mandatory in assessing the poor risk patient. We, of course, also rely on the internist's clinical appraisal of the patient's cardio-respiratory reserve.[10, 11] Ventilatory function is tested by timed vital capacity, maximum breathing capacity, residual air volume and ventilatory reserve. Surely, when vital capacity is below 50 per cent of predicted normal, more pulmonary function studies are indicated. Frequently, differential studies by bronchospirometry are extremely useful and necessary. In general, a patient with maximum breathing capacity of 30L/min. or less is not a likely candidate for any type of major thoracic surgical procedure. The residual capacity is an important determination of the degree of obstructive emphysema and must be closely correlated with the other tests of ventilatory function. We interpret anything greater than 35 per cent volume of residual air indicative of obstructive emphysema and consider the residual air over 50 per cent volume as a grade IV risk. The ventilatory reserve as described by Cournand and Richards[11] is very useful. The normal determination being 90 per cent and anything below 80 per cent indicates rather marked ventilatory deficiency.

The determination of interchanges of gases, although technically more complex and necessitating a rather elaborate cardio-pulmonary staff and physical set-up, is frequently necessary for the critical evaluation of the patient with impaired ventilatory function. These determinations are divided into two major categories: The first, *distribution effect*, alludes to the mechanical factors as responsible agents for decreasing the arterial oxygen saturation. This effect is commonly noted in emphysematous blebs,

complete bronchial obstruction and pulmonary fibrosis. In the second, *diffusion effect*, the factor is one of thickening of the alveolar wall with decrease in diffusion of the oxygen across the barrier into the blood stream.

It is especially important that patients with marginal cardio-respiratory reserve have an expert anesthesiologist as part of the surgical team;[12, 13] also, it is more important to have a skilled anesthesiologist than to quibble about the anesthetic agent. This alert member of the team also carries out the meticulous replacement of fluids and blood. A clean air way during and following operation is of paramount importance in obviating carbon dioxide retention.

IV. Surgical Considerations

As for the surgical considerations, we are firmly convinced of the peculiar safety of isoniazid coverage and have extended our surgical indications and recommendations of definitive procedures for more patients.

Of the collapse procedures, we feel as others[14-19] that the extrapleural method produced the least loss of pulmonary function; however, this procedure was discontinued at National Jewish Hospital more than three years ago because of the serious complication of broncho-extra-pleural fistula.[20] Our procedure of choice today is the extra-periosteal plombage. This operation preserves the good features of the extra-pleural type but usually avoids the serious complications. In the occasional case when it becomes necessary to remove the plombage, we feel the combination of plombage followed by rib resection gives a better collapse with less deformity and less loss of pulmonary function than does the classical thoracoplasty. Frequently, we use plombage collapse not as a definitive procedure but as a preliminary to future excisional surgery. This serves three functions: (1) it allows maximum stabilization of the active disease; (2) frequently obviates residual post-resectional spaces; and (3) prevents over-distention, of whatever importance this may be. From July, 1951, to July, 1953, we employed the Ivalon sponge; however, due to a complication rate of 8.9 per cent of apparently allergic nature, we have changed to Polystan* (polythene) sponges[21] (A/S Ferrosan, Manufacturing Chemists, Copenhagen, Denmark). In the past 11 months, we have inserted 22 of these with only one complication (a tuberculous infection in the sponge space).

When practicable, all significant residual cavitary disease is resected with the purpose of eliminating foci for reactivation and rendering the sputum negative for tubercle bacilli. Furthermore, we believe that resectional surgery conserves pulmonary function to a greater degree than any type of "collapse" therapy. In stable disease, primary resection with tailoring thoracoplasty, if necessary, is becoming the procedure of choice without resorting to preliminary thoracoplasty.

In addition to the common features of anemia, low blood volume, hyperproteinemia, and so forth,[22, 23] we feel that the patient with pulmonary tuberculosis can be classified as a poor risk for surgery because of one or more of the following conditions:

*Distributed in the United States by Lakeside Laboratories, Inc., Milwaukee, Wisconsin.

1. Reduced pulmonary reserve.
2. Highly positive sputum with marked or complete antimicrobial resistance.
3. Infected pleural space with bronchopleural fistula.
4. Extensive bilateral cavitary disease.
5. Extensive pulmonary tuberculosis associated with other serious non-tuberculous diseases.

V. Case Reports

We are presenting a small selected series of cases which serve as illustrative examples of the above categories and will briefly summarize the therapeutic regimen and results.

Dr. M. E. M.: This 56 year old, white physician's first wife died of tuberculosis many years ago. He had a moderately productive cough for many years. In April, 1952, he developed a "cold" with a fever; he was treated conservatively with antimicrobials; however, shortness of breath, increasing productive cough, weight loss and anorexia continued. In July of 1952, chest x-ray film revealed extensive bilateral destructive cavitary tuberculosis and positive sputum. He was treated with streptomycin and PAS until August, 1952; and he was admitted to National Jewish Hospital in September of 1952. X-ray films revealed advanced disease involving all lobes of both lungs with multiple cavitation and pneumonitis replacing the left upper lobe. There was also possible active cavitary disease in the right upper lobe (Fig. 1). Sputum was positive 50/field with 4 plus resistance to isoniazid, but sensitive to streptomycin and PAS. Sedimentation rate was 95 mm./hour corrected. He was continued on streptomycin, PAS and isoniazid (4 mgm./kilo/day); however, he tolerated all drugs poorly (nausea, persistent vomiting, and severe pruritus) and medication was only intermittent. Pulmonary function studies revealed maximum breathing capacity 57 L/min., residual air volume 41 per cent, oxygen saturation 87 per cent at rest, 92.5 per cent after exercise. When he failed to show any appreciable improvement, it was felt some stabilizing procedure should be done. Accordingly, on March 4, 1953, a left Ivalon plombage thoracoplasty (seventh rib posteriorly and third rib anteriorly) was performed. Postoperatively, he did well and was completely ambulated by the 10th day; however, three weeks post-operatively he developed evidence of arteriolo-occlusive disease of his right foot which was treated vigorously with para-vertebral sympathetic blocks and priscoline with marked improvement. Sympathectomy was refused. In spite of his dramatic subjective improvement, his sputum remained heavily positive; and it was felt that definitive resectional surgery could convert his sputum to negativity and thus hasten earlier discharge. Accordingly, on September 23, 1953, resection of the apical posterior and anterior segments of the left upper lobe and superior segment of the left lower lobe was carried out (Fig. 2). Pulmonary functions prior to this second

FIGURE 1

FIGURE 2

procedure were essentially unchanged from previous determinations. Post-operative course was uneventful until the 10th post-operative day when he again developed progressive arteriolo-occlusive disease of his right foot. Conservative measures were of little avail and lumbar sympathectomy was decided on. This was attempted under spinal anesthesia on October 13, 1953; however, cardiac arrest occurred; resuscitation was carried out but the patient remained in coma and expired 13 days after cardiac resuscitation. This case presents a patient with extensive bilateral cavitary pulmonary tuberculosis associated with a serious non-tuberculous disease in whom a stabilizing plombage thoracoplasty brought about marked subjective improvement. The unfortunate accident occurred during the attempt to deal with the serious complicating non-tuberculous disease. This serves as an example of a case in whom efforts were directed toward a cure rather than accepting a so-called "good chronic."

S. L.: This 26 year old, white female had contact with a friend who died of tuberculosis in 1948. She had pleurisy with effusion in 1950 and developed moderately productive cough, weight loss, fatigue and anorexia. Chest x-ray film in 1950 in Israel revealed cavitary tuberculosis of left upper lobe. She was admitted to a sanatorium for seven months where she received streptomycin and PAS for 30 days. Radical collapse was recommended since new huge cavities were noted in the right upper lobe. She refused surgery. Sputum was heavily positive and the sedimentation rate was 74 mm./hr. corrected. Intrapleural adhesions precluded pneumothorax and extrapleural pneumothorax on left was begun and refilled for over a period of a year. She was admitted to the National Jewish Hospital on November 27, 1952, where x-ray film revealed extensive involvement with fibrocavernous disease of the left upper lobe and apparent residual of an extrapleural pneumothorax and multiple fibrocalcific seedings on all lobes bilaterally (Fig. 3). Sputum was positive 40/field; sedimentation rate was 75 mm./hr. corrected; and there was 4 plus resistance to streptomycin and isoniazid. In the hospital she ran an intermittent febrile course with spikes up to 104° F. Aspiration of the extrapleural space revealed no significant bacteriologic findings. She was started on isoniazid and PAS. Pulmonary functions shortly after admission revealed vital capacity of 1460 cc. (40 per cent of normal), maximum breathing capacity of 47 L/min. (55 per cent of normal), residual air volume of 60.6 per cent, alveolar nitrogen (seven minutes of breathing oxygen) 4.3 volume per cent (normal, less than 2½ per cent), alveolar CO_2 8.1 volume per cent (normal, less than 5 per cent), arterial oxygen saturation 92 per cent (rest), 90 per cent (exercise). On March 30, 1953, left extraperiosteal Ivalon plombage thoracoplasty (sixth rib posteriorly and second rib anteriorly) was done. During the next 10 days, massive fluid accumulated in the sponge space with pain, fever, and increase in cough; multiple aspiration with penicillin-streptomycin instillations were to no avail. Aspirated fluid after many cultures was finally positive for tuberculosis. The sponge was removed and collapse maintained with a six and one-half rib resection and partial scapulectomy. She then did well with the right upper lobe lesion controlled; however, an open cavity in the left upper lobe beneath the thoracoplasty remained causing positive sputum, 15/field. Bronchospirometry at this time showed practically no pulmonary function on left. Isoniazid was increased to 8 mgm./kilo/day; and a left pneumonectomy on April 14, 1954, converted her to

FIGURE 3

FIGURE 4

negativity for the first time (Fig. 4). Her pulmonary function studies after the last procedure revealed a slight decrease in all determinations. This case characterizes one with extremely poor pulmonary function and heavily positive sputum with complete antimicrobial resistance. Careful evaluation of the pulmonary function determinations led us to believe that she would successfully withstand surgery.

W. A.: This 24 year old, white female's father was in a tuberculosis hospital at the time of her admission to National Jewish Hospital. Her mother died of tuberculosis in 1934, and one brother died of tuberculous cervical adenitis. At the age of 10 (1940), following an appendectomy, chest x-ray film revealed infiltration in both apices. A diagnosis of pulmonary tuberculosis was made and she was sent to a state sanatorium for six months and treated with bed rest. She was relatively well until 1946 at which time she married, and shortly thereafter developed chronic productive cough with left pleurisy. Annual x-ray films were presumably negative until 1951 when cavitary disease was noted on the left. She was then sent to another state sanatorium for seven months and treated intermittently with streptomycin and PAS. She entered National Jewish Hospital in September, 1952, where x-ray film revealed far advanced bilateral tuberculosis with a large cavity of the right upper lobe and a huge cavity occupying the left upper lobe (Fig. 5). She had heavily positive sputum, was 1 plus resistant to streptomycin, showed clubbing of fingers and the sedimentation rate was 90 mm./hr. corrected. Treatment consisted of streptomycin, PAS and isoniazid. She ran an intermittent fever up to 103° F. In order to gain control of the disease, a left plombage thoracoplasty (seventh rib posteriorly and third rib anteriorly) was done in January of 1953. She then developed marked reaction with fluid formation in the sponge space, necessitating removal of the sponge and rib resection (Fig. 6). Following this, she gradually and progressively improved, became completely ambulatory in six weeks following surgery, has since turned sputum negative and is now on a six hour daily work tolerance. The right-sided cavitary lesion has improved to the point where by tomography no demonstrable cavity is noted. Pre-operatively her pulmonary functions showed a maximum breathing capacity of 61 L/min., vital capacity of 1600 cc., and a residual air volume of 54 per cent; bronchospirometry revealed equal function bilaterally. Oxygen saturation at rest was 87.9 per cent and 90.8 per cent after exercise. Post-operatively her pulmonary functions showed no appreciable change after plombage; however, her maximum breathing capacity fell to 48 L/min. after the rib resection. The vital capacity after the rib resection was 1300 cc. with a 55 per cent residual air volume. This case represents an individual with extensive bilateral cavitary disease which responded with a salutory effect after a stabilizing procedure and antimicrobials.

E. L.: This 37 year old, white male was admitted to National Jewish Hospital on December 22, 1951, with a history of having a diagnosis of tuberculous bronchiectasis of the right upper lobe confirmed with a bronchogram in 1941. He was treated with bed rest for a period of about nine months at that time; his sputum was negative. He was discharged to work and gradually increased his activity. He had been actively working for about 10 years prior to admission; however, he had never felt well since the original disease. In June of 1950 he broke down with right upper lobe disease and

FIGURE 5 FIGURE 6

also had new spread to the left upper lobe. At that time he had positive sputum. Treatment consisted of streptomycin and PAS for a period of about 14 months, and also pneumoperitoneum for four months; on this regime he improved. He was admitted to National Jewish Hospital for more definitive therapy on December 22, 1951. Shortly after admission, he had one bout of two ounce hemoptysis; he was placed on streptomycin, PAS and tibione. X-ray film revealed extensive bilateral cavitary pulmonary tuberculosis with multiple seeding throughout all lobes both lungs (Fig. 7). The pneumoperitoneum was continued for a short time and later abandoned. He improved slightly on this conservative therapy but still had a heavily positive sputum, 55/field. Pulmonary functions revealed maximum breathing capacity of 113 L/min., with vital capacity of 2950 cc.; bronchospirometry revealed right-sided vital capacity to be 48 per cent and oxygen consumption on the right 78 per cent with a minute volume of 47 on the right. Several surgical procedures, consisting of bilateral plombage with possible bilateral resection of the cavitary residua, were recommended to bring the disease under control and act as definitive therapy. On August 25, 1952, extraperiosteal plombage thoracoplasty on the right (sixth rib posteriorly and second rib anteriorly) was carried out. His sputum remained heavily positive and four months later left-sided extraperiosteal plombage thoracoplasty (sixth rib posteriorly and third rib anteriorly) was done. His sputum still remained heavily positive; accordingly, two months later, right upper lobectomy was performed (Fig. 8). Following this procedure he became negative on February 5, 1953 and remained so until discharge in June of 1953. His pulmonary functions after all these procedures were markedly preserved with only a slight drop in all determinations. This case presents one with extensive bilateral cavitary pulmonary tuberculosis in whom a long-range multiple surgical program was outlined and satisfactorily concluded with remarkable preservation of pulmonary functions.

DISCUSSION AND SUMMARY

At the National Jewish Hospital, we have observed a marked decrease in the percentage of patients with minimal to moderately advanced exudative disease. Those with far advanced fibrocavernous lesions are now our principal concern. These changes in the patient population of our institution together with the more perfectionistic demands as to the results of treatment have necessitated development of the "team concept" of therapy with close coordination between the internist, bacteriologist, physiologist, and surgeon.

As a result of recent advances in chemotherapy, many poor risk patients can now more safely be submitted to definitive major surgical procedures aimed at completing the control of tuberculosis which cannot be achieved

FIGURE 7 FIGURE 8

by drugs alone. It is our experience that in the patient with isoniazid-resistant, catalase-negative tubercle bacilli, the risk of serious post-operative spread of disease is minimal or absent.

Thus, careful evaluation of the cardio-respiratory system as to the type and extent of pulmonary insufficiency takes on an even greater importance in selecting patients for major thoracic surgical procedures. In other words, the "tuberculous process" per se is no longer of as much importance as a contraindication for surgery.

Our experience with a wide variety of surgical procedures indicates that broader application of resectional surgery under coverage of isoniazid is now possible and, indeed, definitely indicated to control pulmonary tuberculosis more completely so that a maximum number of patients can be returned earlier to useful lives.

RESUMEN

Se ha notado una disminución de enfermos de tuberculosis mínima o moderadamente evanzada en el National Jewish Hospital.

Los enfermos con tuberculosis fibrocabernosa muy avanzada son ahora neustra principal preocupación.

Estos cambios en la problación así como las demandas perfeccionistas de resultados del tratamiento han necesitado el desarrollo de un "concepto de equipo" de tratamiento con colaboración muy estrecha entre el internista, el bacteriólogo, el fisiólogo y el cirujano.

Como resultado de los adelantos recientes en quimioterapia muchos enfermos que eran malos riesgos pueden ahora ser sometidos con seguridad a la cirugía mayor encaminada a controlar la tuberculosis que no puede dominarse por las drogas solas.

Según nuestra experiencia el enformo con isoniacido-resistencia catalasas-negativas al bacilo de Koch, el riesgo de diseminación grave postoperatoria es mínimo o nulo.

Así, la valuación cuidadosa de los aparatos respiratorio y circulatorio en lo referente al tipo y extensión de la insuficiencia pulmonar tiene mucho mayor importancia para escoger los enfermos para la cirurgía mayor torácica. En otras palabras, el "proceso tuberculoso" per se ya no es una contraindicación de gran importancia para la cirugía.

Nuestra experiencia con una gran variedad de procedimientos quirúrgico indica que ahora es posible y sin duda definitivamente indicado el controlar la tuberculosis más completamente de manera que un número máximo de enfermos pueden reintegrarse más pronto a la vida útil.

RESUME

A l'hôpital National Israélite, les auteurs ont observé un déclin marqué du pourcentage des malades atteints de lésions exsudatives, allant d'une atteinte minime à une forme modérément avancée. Les malades atteints de lésions fibro-cavitaires très denses constituent maintenant leur principal souci. Ces modifications dans le type de malades de leur établissement

ajoutées aux nécessités de perfectionner encore davantage les résultats du traitement, ont exigé le développement du "concept d'équipe," avec collaboration étroite entre le médecin, le bactériologiste, le physiologiste et le chirurgien.

Par suite des récents progrès de la chimiothérapie; beaucoup de malades sérieusement atteints peuvent maintenant subir avec beaucoup plus de sécurité les interventions de grand chirurgie. Leur but est d'obtenir une guérison de la tuberculose qui n'a pas pu être réalisée par les drogues seules. D'après l'expérience des auteurs, les bacilles résistants à l'isoniazide catalase-négatives ne font courir au malade qui en est porteur qu'un risque minime ou même inexistant de dissémination post-opératoire.

L'étude minutieuse du système cardio-respiratoire pour évaluer le type et l'étendue de l'insuffisance pulmonaire, prend même une importance de plus en plus marquée pour décider quels malades sont justiciables de la grande chirurgie thoracique. En d'autres termes, le "processus tuberculeux" en lui-même n'est plus d'une importance telle qu'il puisse être une contre-indication à la chirurgie.

L'expérience des auteurs portant sur une grande variété de méthodes chirurgicales, démontre qu'une plus large application de la chirurgie d'exérèse sous le couvert de l'isoniazide est maintenant possible et même definitivement indiquée pour juguler plus complètement la tuberculos pulmonaire. Ainsi sera rendu plus précocément à une existence utile le plus grand nombre possible de malades.

ZUSAMMENFASSUNG

Im Nationalen Jüdischen Krankenhaus haben wir eine deutliche Abnahme des Prozentsatzes von Patienten mit geringfügiger oder mässig fortgeschrittener Tuberkulose gefunden. Jetzt haben wir vorzugsweise Kranke mit fortgeschrittenen fibrokavernösen Veränderungen in unserer Behandlung. Diese Veränderungen in der Zusammensetzung unseres Patientengutes, zusammen mit den höheren Ansprüchen hinsichtlich der Behandlungsergebnisse, haben die Entwicklung eines "Team-Begriffes" für die Therapie geschaffen unter enger Zusammenarbeit von Internisten, Bakteriologen, Physiologen und Chirurgen.

Auf Grund der Fortschritte in der Chemotherapie können heute viele Patienten, die früher nicht ohne Risiko operiert werden konnten, leichter grösseren operativen Eingriffen zugeführt werden. Auf diese Weise ist es möglich Tuberkulose nachhaltiger zu behandeln. Nach unserer Erfahrung ist die Gefahr einer ernsten postoperativen Ausbreitung der Krankheit bei Patienten mit isoniazid-resisten, katalasenegativen Tuberkelbakterien gering.

Zur Auswahl der Patienten für grosse chirurgische Eingriffe ist eine sorgfältige Prüfung der cardio-respiratorischen Funktion erforderlich, um Art und Ausdehnung einer respiratorischen Funktionsbehinderung zu beurteilen. Mit anderen Worten ist der "tuberkulöse Prozess" an sich nicht mehr von so grosser Bedeutung als Kontraindikation gegen eine chirurgische Behandlung.

Unsere Erfahrungen mit den verschiedensten chirurgischen Eingriffen zeigen uns, dass unter Isoniazid-Behandlung eine weitere Anwendung der Resektionstherapie möglich ist, und dass tatsächlich die Lungentuberkulose heute besser beherrscht werden kann. Daher ist eine grössere Anzahl von Patienten heute eher einem nützlichen Leben zuzuführen.

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Sarcoidosis: Pulmonary and Skin Studies Before and After ACTH and Cortisone Therapy†

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Sarcoidosis, when entertained as a possible diagnosis today, has a vastly more extended significance than when the term "Sarcoid" was first used by Boeck[1] in 1899 to describe the skin lesions. Sarcoidosis is more and more frequently considered in the differential diagnosis of obscure systemic illness. The present, most widely accepted, concept of sarcoidosis is that it is essentially a systemic disease which may involve not only skin and subcutaneous tissue, but also lymph nodes, eyes, bones and viscera, especially the lungs.

The characteristic, although non-specific, microscopic lesion of sarcoidosis is a granuloma composed of nests of epithelioid cells.[2, 3] In the later stages, giant cells of either the Langhans or foreign body type are often present; the latter frequently contain inclusing bodies of round (Schaumann) or stellate ("asteroid")[4] configuration. In systemic sarcoidosis, such granulomata may be found in almost any organ or tissue, but they have a predilection for skin, lymph nodes, spleen, liver, lungs, salivary glands, bone and eye. The granulomata may be contiguous, but are rarely confluent, and they almost never caseate in the manner which is characteristic of tuberculosis.

The granuloma of sarcoidosis has a cycle of variable duration, beginning with the appearance of perivascular inflammatory cells, progressing to the formation of an epithelial granuloma, which eventually disappears or is replaced by fibrosis, about a core of collagenous hyaline material. Generally, a number of granulomata of about the same stage will be found in a given specimen.

The principal pulmonary complications and sequellae of sarcoidosis that are found at post mortem examination include fibrosis and cyst formation; only rarely is there cavitation, bronchiectasis or emphysema. Tuberculosis is found in 10 per cent or more of clinical cases and with

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FIGURE 1 FIGURE 2 FIGURE 3

Figure 1 (Case 1): Skin lesion on cheek shows typical discrete and confluent tubercules throughout the corium, composed of epithelioid cells with a narrow zone of lymphocytes at the peripheries. Giant cells are absent, and there is no caseation necrosis. The nest of epithelioid cells are separated by connective tissue. The overlying epidermis, not seen here, is atrophic.—*Figure 2* (Case 1): There is an increase in the normal lung markings bilaterally, multiple minute areas of density throughout both lung fields, small calcific foci in the left and right mid-lung fields. There is moderate enlargement of the hilar and tracheo-bronchial nodes bilaterally. Impression: Bilateral hilar and tracheo-bronchial adenopathy with increase in pulmonary markings, consistent with the clinical diagnosis of sarcoidosis.—*Figure 3* (Case 1): Re-examination after treatment with ACTH shows a decrease in the previously described hilar adenopathy, especially marked on the right; otherwise, the examination is essentially unchanged.

much greater frequency in autopsy material.[5] The question of the relation between tuberculosis and sarcoidosis is still an open one; this problem is particularly significant in the American negro. Carmen C. Thomas,[6] in a study of sarcoidosis in the negro, felt that this is a systemic disease whose relation to tuberculosis is still obscure, even though she found a high incidence of pulmonary involvement.

Clinically, the disease tends to be remittent, with one or more active phases of granuloma formation, lasting for a variable duration of from weeks to years. When systemic, activity of the disease is characterized by constitutional symptoms of low grade fever, malaise, fatigue, and occasionally erythema nodosum. At such times the serum globulin level will usually be elevated and evidence of involvement of a specific organ or organs may appear. Remission or recovery is indicated by a return of strength and well being, a decrease in the serum globulin concentration to the normal range and by the partial or complete subsidence of the manifestations of specific organ involvement. Residua are determined by the damage to host cells and by the amount of fibrosis that has developed during healing.

In most patients with systemic sarcoidosis, granulomata eventually infiltrate the lung sufficiently to produce x-ray abnormalities. These persist for a variable period of time, from several weeks to many years.[7] Two types of parenchymal involvement appear, either alone or in combination. In one, the granulomata produce scattered miliary or nodular shadows; in the other, by following the course of small blood vessels and lymphatics, they form a reticular pattern on the film, usually extending out from either hilus. Reisner stated that the latter type of distribution is more likely to be seen later in the course of the disease, and that it is more frequently followed by fibrosis.[8] Either process may be generalized, or may be restricted to local areas such as the basal portions or inner and middle zones. It need not be symmetrical, but usually is. Hilar adenopathy is commonly seen, and classically is bilateral, with enlargement of paratracheal as well as peribronchial nodes.

These structural alterations in the lungs, together with the sarcoid granulomata themselves, are responsible for the alterations in pulmonary function to be found in sarcoidosis. In general, three patterns of pulmonary dysfunction have been described:[9] One, in which all lung volumes are reduced, but gas exchange is unhampered; a second, in which the major disturbance is in gas exchange across alveolar-capillary membranes; a third, in which the pattern of pulmonary emphysema is mimicked with a greatly increased residual volume.

The use of ACTH and cortisone, chiefly the latter, in the treatment of pulmonary sarcoidosis has been reported by several authors since 1951,[9, 10, 11] but few studies and accurate measurements of pulmonary function before and after therapy have been reported. No clear picture of the indications for, or dangers of hormonal therapy in pulmonary sarcoidosis has emerged up to the present time. Problems that face the therapist include the use of a potent and sometimes dangerous drug in a relatively benign con-

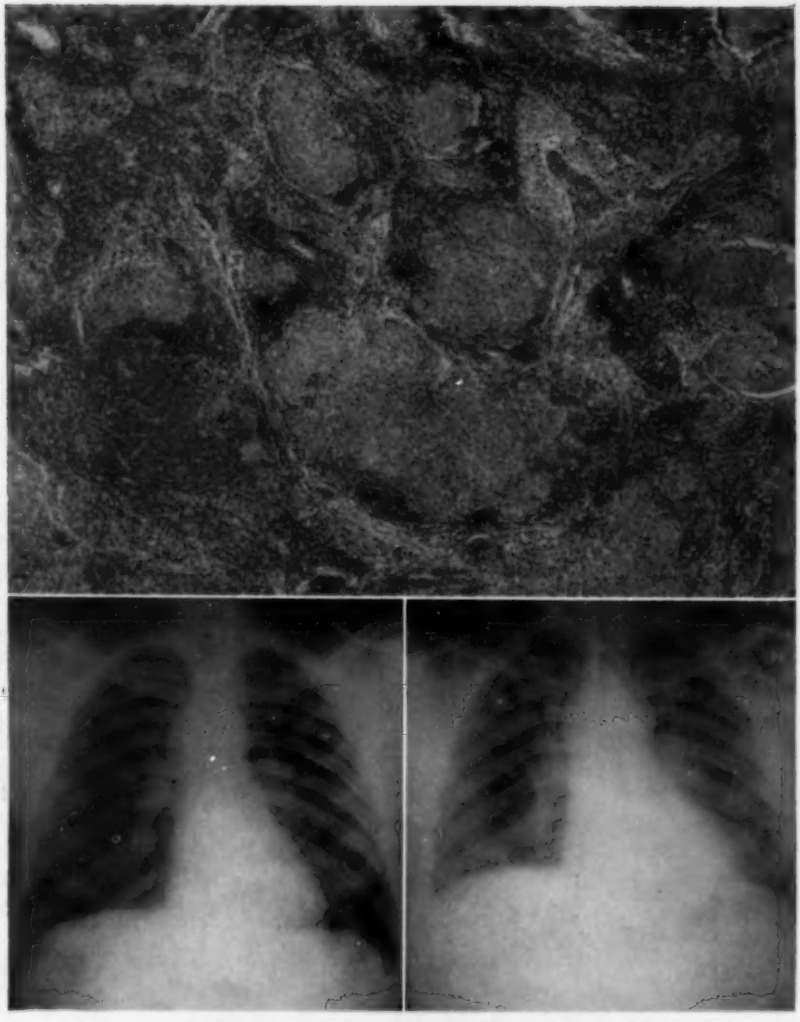

FIG. 4

FIGURE 5

FIGURE 6

Figure 4 (Case 2): The nodal architecture is destroyed due to the presence of numerous discrete and confluent granulomatous lesions. These lesions consist of large, pink cells with abundant cytoplasm, in closely packed and frequently swirling or laminated arrangements. Multinucleated giant cells, of the Langhans variety, are seen more numerously in the centers of these granulomata. Caseation is absent. Because of low magnification, the rare, intracellular inclusion bodies of the asteroid or spiculated type which are present, cannot be seen.—*Figure 5* (Case 2): There is a minimal increase in lung markings with an associated bilateral hilar enlargement, most marked on the left. There is widening of the superior mediastinum on the right, by a convex area of increased density which appears continuous with the aorta. The trachea is in the midline. Impression: Bilateral, hilar adenopathy, with increase in pulmonary markings. The right mediastinal density appears to be a tracheo-bronchial node. The findings are consistent with the clinical diagnosis of sarcoidosis.—*Figure 6* (Case 2): Re-examination after treatment with ACTH shows the adenopathy as in Fig. 5. There appears to be a slight increase in the right hilar adenopathy with no appreciable change on the left. The right mediastinal density is likewise slightly increased in size. Impression: Slight increase in the right hilar and tracheo-bronchial adenopathy.

dition,[12] the possibility of causing an increasing pulmonary fibrosis with therapy,[11] and the possibility of accelerating or activating a tuberculous process.

Present Study

In this paper, we report our observations on the effects of ACTH and cortisone therapy in five patients with systemic sarcoidosis involving the lungs.

The diagnosis was confirmed by skin biopsies in three patients and by lymph node and spleen biopsies in each of the others. The three females and two males, all manifested signs and symptoms of active disease. Clinical studies to exclude the possibility of tuberculosis were performed on each of the patients. Chest x-ray studies, electrocardiograms, skin tests, chemical blood examination and pulmonary function studies[13, 15] were carried out before and after treatment.

Treatment

ACTH was given to four and cortisone, to one.

The course of treatment ranged from 35 to 45 days. Each patient was given 80 units of H.P. (highly purified) ACTH gel* intramuscularly daily, and the dose was gradually decreased toward the end of the treatment. The total dose for each one was from 1500 to 2000 units. The patient treated with cortisone** was started on an initial dose of 300 mg. orally, for the first three days, 200 mg. for five days and then 100 mg. daily for the remaining 34 days. The total dose was 5,300 mg.

During the entire course of treatment, all were on a low salt diet and were given supplemental potassium chloride, orally. Three were given 600,000 units of aqueous crystalline suspension of procaine penicillin, intramuscularly, daily, and the other two received 1 gram Terramycin*** daily by mouth. Two with positive tuberculin test were given, in addition, 1 gram of streptomycin,** intramuscularly, twice a week during the course of treatment and for six weeks thereafter. This was done as a precautionary measure against a possible activation of a tuberculous process, even though there was no evidence of any such process.

*Kindly supplied by the Armour Laboratories, Chicago, Illinois.

**Kindly supplied by Merck and Co., Inc., Rahway, New Jersey.

***Kindly supplied by Chas. Pfizer & Co., Inc., New York, New York.

Case Histories

Case 1: O. D., a 33 year old negro housewife, was first seen in the summer of 1949 because of a crusted nodule on her left malar area of over three months' duration. Biopsy was consistent with sarcoidosis. The lesion, an irregular, superficially ulcerated nodule 1.5 cm. in diameter, became slightly larger over a three-year period and was excised in December 1952. A few months later, there was a recurrence in the scar, and she noted the onset of gradual weight loss and persistent, dry cough.

Laboratory studies revealed normal urinalysis and blood counts. The albumin to globulin ratio in the serum was 1.8/4.8. Histoplasmin, coccidiomycin, lepromin and tuberculin (1:10,000 old tuberculin) skin tests were negative. The intradermal sarcoidosis (Nickerson-Kveim) test was positive. Skin biopsy of the recurrent cheek lesion was consistent with sarcoidosis (Fig. 1). The electrocardiogram was normal. Chest x-ray film (Fig. 2) showed multiple minute areas of density throughout both lung fields and prominence of hilar nodes bilaterally, consistent with sarcoidosis. No bone change was seen by x-ray film.

In March 1953, she was started on a 42-day course of ACTH. During treatment she

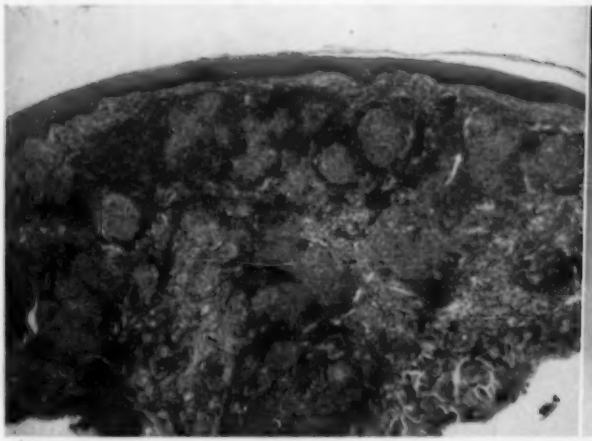

FIGURE 7

FIGURE 8

FIGURE 9

Figure 7 (Case 3): There are many typical, discrete and confluent tubercles throughout the entire corium, forming nests of epithelioid cells with occasional Langhans type giant cells and dense, narrow zones of lymphocytes around their peripheries. There is no caseation necrosis. The rete pegs of the epidermis and the dermal papillae are flattened by the subjacent reaction.—*Figure 8* (Case 3): Subapical adhesions are present bilaterally. Increased linear markings are present throughout both lung fields, consistent with peribronchial thickening or old fibrosis. The mediastinal shadow is not remarkable. Impression: Findings are consistent with chronic inflammatory changes.—*Figure 9* (Case 3): Re-examination after treatment with ACTH shows no essential changes.

had increase in appetite and gain in weight. She felt better, tired less quickly, noted less cough and less dyspnea. The skin lesion on her face healed completely, leaving only a small scar. Laboratory studies following treatment showed reversal of albumin-globulin ratio to normal, 3.3/2.8. X-ray film showed definite, though slight, decrease in size of the hilar nodes and less prominence of the linear markings over both lung fields (Fig. 3). Her condition continued to improve during the follow-up period of six months. Recently, however, the site of the previous skin lesion over the left malar area is again showing clinical evidence of reactivation. This is approximately six months after cessation of treatment with ACTH.

Case 2: C. M., a 27 year old negro laborer, was seen in March 1953 because two months previously he had developed pain and blurring of vision of both eyes, followed by swelling and inflammation, diagnosed acute iritis. One week before admission, he had polyuria, stiffness of the left shoulder and arm, and swelling of his left eye. He had blurring of vision of the left eye, and the left pupil was slightly larger than the right. There was an acneiform eruption over his back.

Laboratory studies revealed normal blood counts, blood chemistry examinations and urinalyses. Tuberculin (1:1,000 old tuberculin) histoplasmin, coccidiomycin, lepromin and the intradermal sarcoidosis skin tests were negative. Chest x-ray film revealed enlarged hilar lymph nodes (Fig. 5). A left mediastinal lymph node biopsy showed a granulomatous lesion strongly suggestive of sarcoidosis (Fig. 4). All studies were negative for tubercle bacilli.

In April 1953, a 45-day course of ACTH as described above was started. This was followed by less dyspnea, and his cough subsided. X-ray film after treatment, however, showed a slight increase in size of the hilar nodes, and an increase in the tracheobronchial markings (Fig. 6). There was complete clearance of the inflammatory process involving both eyes.

During six months following treatment, his improved condition remained stable except for a brief episode of acute bronchitis which cleared with penicillin.

Case 3: M. B., a 56 year old white housewife, was admitted in April 1952, when right nephrectomy was performed because of nephrolithiasis and secondary infection. In the post-operative convalescence, she developed left facial nerve paralysis, associated with a tender and enlarged parotid gland. In July 1952, she developed persistent vesiculation, ulceration and inflammation of the left half of her lower lip.

In April 1953, examination revealed residual left peripheral facial nerve paralysis; there was a medium red, indurated lesion of the left side of the lower lip, definitely but not sharply outlined, about 2.0 cm. in diameter, involving the vermillion and glabrous portion of the lip. The left parotid gland was enlarged and rubbery in consistency, and two small nodules were present in the left submaxillary region. The heart was within normal limits, and no murmur was heard. The blood pressure was 180/100, and the pulse, 80. There were dry and sibilant rales over both lung fields.

Laboratory studies revealed normal blood counts and urinalysis. The serum albumin-globulin ratio was 2.2/4.2. X-ray film of the bones showed osteoporosis and a circumscribed area of increased radiance, 1 cm. in diameter, in the central portion of the proximal phalanx of the right first toe, consistent with sarcoidosis. Biopsy from the lip (Fig. 7) revealed a granuloma consistent with sarcoidosis. Acid-fast stains, cultures and guinea pig inoculations of pulmonary secretions and from the biopsy specimens were negative for tubercle bacilli. Skin test with old tuberculin 1:10,000 was negative, and 1:1,000 was slightly positive. The intradermal sarcoidosis test was positive. Histoplasmin, coccidiomycin and lepromin tests were negative.

In April 1953, a 35-day course of ACTH, as described above, was instituted and was followed by marked symptomatic improvement. The swelling of the left parotid gland and the two submaxillary nodes decreased and were no longer palpable. The lesion on the lip healed completely, leaving a pale, flat scar. The albumin-globulin ratio changed to 3.8/2.4. These restorations to normal were maintained during the many months of post-therapy observation. However, roentgenological examinations of the lungs showed no demonstrable change of the subapical adhesions and increased linear markings (Figs. 8 and 9).

Case 4: J. O'N., a 64 year old white carpenter, had repeated admissions to The Boston City Hospital since 1940 because of recurrent pulmonary infections. On each admission he had hepatosplenomegaly; during the past four years, he also had chronic iritis and iridocyclitis. Repeated chest x-ray films showed increased bronchovascular markings and prominent hila (Fig. 11). Studies for tuberculosis were negative through the years. In January 1953, he had a gastro-intestinal hemorrhage. On admission, examination disclosed impaired vision, scattered rales over the bases of both lungs, enlarged liver and spleen, slight clubbing of the fingers and blood pressure of 170/95. Hemorrhage was attributed to bleeding esophageal varices. Splenectomy and ligation of the varices was performed.

Laboratory studies, two months following this operation, revealed normal blood

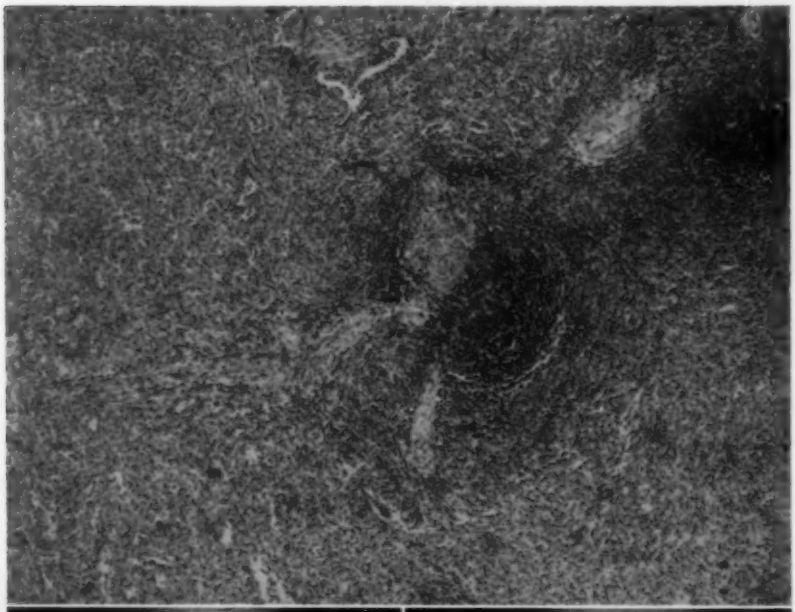

FIG. 10

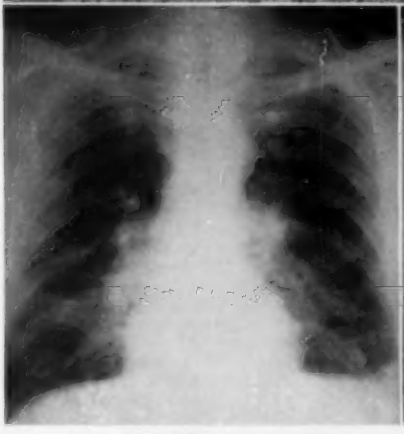

FIGURE 11

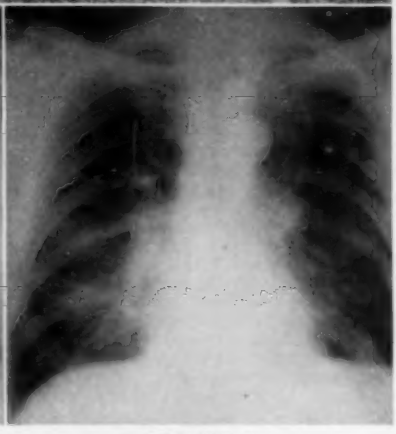

FIGURE 12

Figure 10 (Case 4): Numerous, discrete, granulomatous lesions are seen primarily in or near the sheathed arteries. These lesions consist of aggregates of large, acidophilic cells with abundant cytoplasm. Scattered, multinucleated giant cells of the Langhans type are seen. The lesions are round or oval, compact, and many show varying degrees of fibrosis. Caseous and infarct necrosis are absent.—*Figure 11* (Case 4): There is blunting of both costophrenic angles, especially the left. Diffuse increase in the normal lung markings is present with associated linear strands radiating from both hila, some of which run transversely in the lower lobes. There is a 1 cm. softly-outlined density in the left first anterior interspace with a second similar area at the anterior end of the left first rib. Both hila are increased in size with an irregular, fuzzy margin. The trachea is in the midline. Impression: Bilateral, diffuse, fibrotic infiltrations with hilar adenopathy consistent with the clinical findings of sarcoidosis.—*Figure 12* (Case 4): Re-examination after treatment with *cortisone* shows no appreciable change in the previously described pulmonary findings.

count, hemoglobin of 10.5 gms., normal urinalysis, serum albumin-globulin ratio of 2.4/6.4 and impaired liver function tests. Tests with old tuberculin 1:10,000 were negative and with 1:1,000, positive. Histoplasmin and coccidiomycin tests were negative, lepromin, slightly positive and intradermal sarcoidosis, positive. Histological examination of the spleen showed congestive splenomegaly and miliary granulomata, suggestive of sarcoidosis (Fig. 10). Concentrates, smears and guinea pig inoculations for tubercle bacilli were negative.

In May 1953, he was started on a 42-day course of cortisone, as described above. During treatment, he developed increased hypertension and headaches. However, he experienced marked improvement in his cough and vision. The chest x-ray film showed no change in comparison with previous examinations (Fig. 12). The size of the liver did not seem to decrease materially. He remained subjectively well during the period of observation following the cessation of therapy.

Case 5: M. H., a 56 year old white woman, was referred in May 1953 for special study of sarcoidosis of seven years' duration. At the age of 12 she had sustained a head injury and was completely blind for one year. Since then, the right eye had practically none and the left, fairly good vision. At the age of 25 she had become totally deaf. In 1946, two masses appeared suddenly, without symptoms or preceding trauma, in the skin of the lateral aspect of the left arm just above the elbow and in the anterolateral area immediately below the axillary fold. These lesions, approximately 2 by 1 cm., were medium red and non-tender. Both were excised one year later, and the histological findings were consistent with sarcoidosis. Within the next few years, light brownish-red indurations appeared at the scars and gradually increased in size. Both lesions were again excised (Fig. 13).

Laboratory studies revealed normal blood counts, blood chemistry studies, urinalyses and spinal fluid. Skin tests with 1:1,000 old tuberculin, histoplasmin, coccidiomycin and lepromin were all negative. Blood serum test for syphilis was doubtful in the undiluted serum and negative in other dilutions. The intradermal sarcoidosis skin test was positive to one antigen and negative to antigen made from her own skin lesion. Chest x-ray film showed radiating shadows extending out from both hilar regions, consistent with sarcoidosis (Fig. 14). X-ray films of the hands showed bone changes of the terminal phalanx of the right thumb and several other phalanges of the right hand, consistent with sarcoidosis. Studies for tubercle bacilli were negative.

In May 1953, she was placed on a 40-day course of ACTH as described above. During treatment she experienced marked symptomatic improvement, including vision. In a follow-up period of six months, improvement continued, and she has consistently retained a euphoric sense of restoration of some of her vision and considerable zest of living. The sarcoidosis infiltrates in the skin were all resolved. X-ray film of the chest showed marked clearance in the left lung.

Results

Ocular involvement responded well to treatment. Case 2, who had acute ocular lesions, showed complete remission. Case 4, whose bilateral ocular involvement was present for more than four years and was gradually getting worse, attained considerable improvement in the vision of his left eye, while the right eye remained unimproved because of the presence of extensive scarring. Case 5 had no vision in the right eye for 26 years, considered to be caused by a head injury, and was gradually losing vision in her left eye. Treatment produced considerable benefit. Her vision returned to the right eye to such an extent that she was able to read and was able to go out and walk along the street unassisted.

The skin lesions in Cases 1 and 5, on the face and arms, healed, leaving soft, pale, flat scars. The lymph nodes in the submaxillary regions regressed early in the course of treatment. A large infiltrated lesion of the lower lip in Case 3 healed rapidly, leaving a small, soft, pale scar. The enlarged left parotid gland decreased gradually in size and was impalpable and invisible at the end of the fourth week. The left facial paralysis, however, showed very slight improvement. Cough and dyspnea in Cases 1, 2 and 4 were dramatically improved.

Roentgenographic re-examination after treatment showed no essential

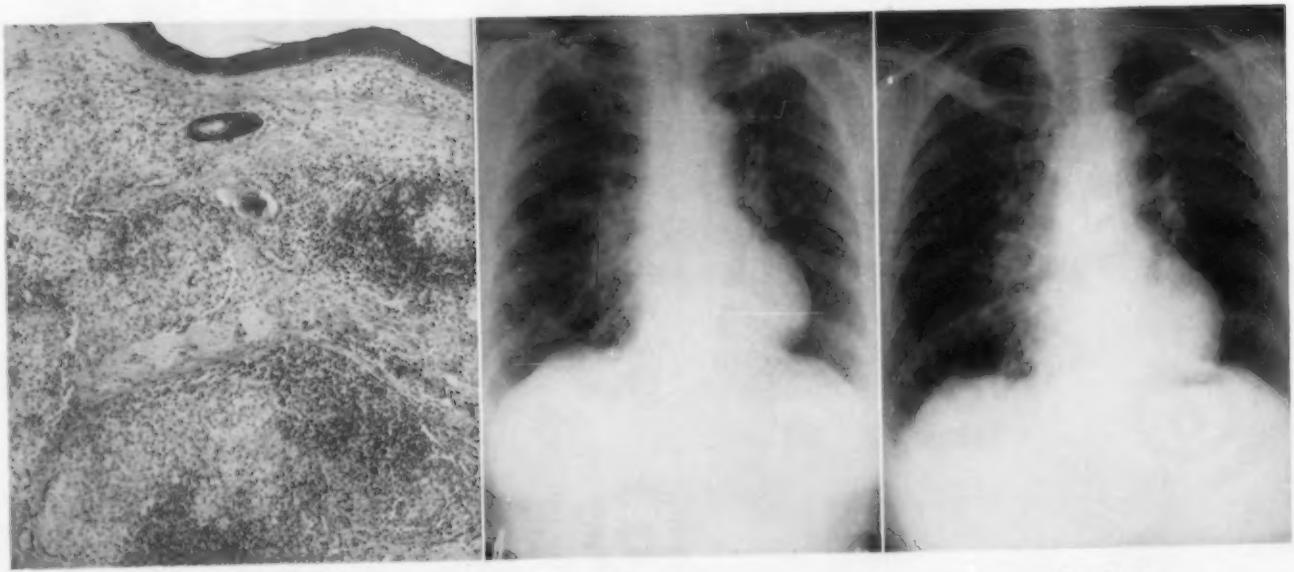

FIGURE 13 FIGURE 14 FIGURE 15

Figure 13 (Case 5): Multiple tubercles are seen throughout the corium, composed of nests of epithelioid cells and a few giant cells, Langhans type, encircled by a narrow zone of lymphocytes. The nests are separated by thin bands of fibrous tissue. Caseation necrosis is absent.—*Figure 14* (Case 5): There are bilateral linear infiltrations, most pronounced in the infraclavicular regions, with some elements of fine nodularity. The remaining markings are increased, and there is bilateral enlargement with lobulation on the right. The trachea is in the midline. Impression: Bilateral, hilar adenopathy, especially on the right, with generalized increased markings and finely nodular and linear infiltrations in both infraclavicular areas. Findings are consistent with sarcoidosis.—*Figure 15* (Case 5): By comparison with previous study, this film shows partial clearing of the infraclavicular mottling. The left hilar adenopathy has entirely disappeared, but no definite changes of the right hilar adenopathy can be seen. Impression: Marked improvement over previous findings.

change of the pulmonary lesions in any of the patients, except in Case 5. Pulmonary and mediastinal lymph nodes were improved in Cases 1 and 5, increased in 2 and unchanged in 3 and 4.

Pulmonary Function Studies

1. Lung Volume Measurements (Table I)

Before treatment, several of the lung volumes showed slight to moderate deviations from the normal range. The tidal volume was elevated in Cases 1, 3 and 4. The vital capacity was moderately decreased in Case 3. The residual volume was significantly elevated in Case 4 only and the total lung capacity was within normal range. Case 1 could not cooperate sufficiently to make the determinations of residual volume and total lung capacity valid.

After treatment, moderate and variable changes were recorded in several patients. The tidal volumes decreased 44 per cent and 29 per cent in Cases 1 and 3 respectively but increased 40 per cent and 15 per cent in Cases 2 and 4 respectively. The vital capacity improved 19 per cent in Case 2. The residual volume increased 28 per cent in Case 2 and decreased 24 per cent in Case 3. The total lung capacity showed an increase of 20 per cent in Case 2 and 10 per cent decrease in Case 3.

The *ratio of residual volume to total lung capacity* is considered normal up to 30.8 per cent,[13] while others[14] considered a value of 40.9 per cent normal for persons above the age of 50 years. Three of the patients studied were 55 years and older, and their ratio ranged between 40.4 per cent and 44.5 per cent. Another who was 27 years old had a ratio of 31.2 per cent. The changes after treatment were minimal except in Case 3, where the ratio decreased from 44.5 per cent to 39.3 per cent.

2. Ventilation Studies (Table II)

Before treatment, several patients had abnormal ventilation values. The respiratory rate was slightly increased in Cases 1 and 5. The resting ventilation was high in Case 1. The maximal breathing capacity was

TABLE I—LUNG VOLUME MEASUREMENTS

Pat., Age Sex, Color		B. S., m^2	Tid. Vol. (L)	Vit. Cap. (L)	% Pred. V. C.	Resid. Vol. (L)	Tot. Lung Cap. (L)	% Pred. T. L. C.	$\frac{\text{R. V.}}{\text{T. L. C.}} \times 100$
1. O. D., 37 Fem., Negr.	Before Rx	1.49	.834	2.950	102.18				
	After Rx	1.54	.465	2.843	98.48				
2. C. M., 28 Male, Negr.	Before Rx	1.83	.520	4.180	100.36	1.895	6.095	117.0	31.20
	After Rx	1.88	.729	4.954	118.97	2.421	7.375	119.0	32.83
3. M. B., 55 Fem., Wh.	Before Rx	1.48	.913	2.153	87.31	1.724	3.877	105.3	44.47
	After Rx	1.54	.646	2.023	82.04	1.308	3.331	94.0	39.27
4. J. O'N., 65 Male, Wh.	Before Rx	1.92	.700	3.933	106.00	2.671	6.604	116.0	40.45
	After Rx	1.96	.807	3.964	107.24	2.654	6.622	115.5	40.08
5. M. H., 56 Fem., Wh.	Before Rx	1.66	.435	2.551	95.90	2.044	4.595	119.5	44.50
	After Rx	1.68	.403	2.465	92.33	2.105	4.561	119.0	46.15

impaired in Cases 2 and 3. The ventilatory reserve was slightly diminished in all patients. The index of intrapulmonary mixing was normal in all patients.

After treatment, all patients with disturbed ventilatory functions showed improvement. The maximal breathing capacity remained decreased in Case 2 and the ventilatory reserve remained slightly below normal values (95 per cent) in all patients.

3. Alveolar Gases and Arterial Blood Gas Analyses (Table III)

The pCO_2 and pO_2 of the alveolar gases were within normal range before and after therapy.

The arterial blood values were determined before and after standard exercise. Before treatment, slight hypoxia was observed in Cases 3, 4 and 5; this improved after exercise except in Case 5. The CO_2 content and the pH were well within normal range in all patients before and after exercise.

After treatment, Case 5 showed good oxygenation; Case 1, who had normal saturation before treatment, now showed moderate hypoxia, and the others showed minor changes. The CO_2 content and pH remained within normal range except for Case 5 who had a borderline CO_2 content after therapy.

TABLE II—VENTILATION STUDIES

Patient		Resp. Rate	Rest. Vent. L/min.	Maximal Breathing Capacity L/min.	Maximal Breathing Capacity % Pred.	Vent. Res. %	Index of I. P. Mixing (%N)
1. O. D.	Before Rx	20	11.19	88.34	110.25	81.12	
	After Rx	15	4.53	95.03	103.64	92.66	
2. C. M.	Before Rx	16	4.55	122.00	92.75	93.18	1.08
	After Rx	12	4.65	122.56	90.69	92.87	1.72
3. M. B.	Before Rx	9	5.55	55.94	83.57	85.32	1.50
	After Rx	10	4.20	76.45	109.08	91.55	1.52
4. J. O'N.	Before Rx	13	4.61	100.93	113.00	89.00	2.50
	After Rx	13	4.80	103.04	112.99	90.00	2.47
5. M. H.	Before Rx	17	4.45	93.51	126.80	92.10	1.66
	After Rx	18	4.31	92.65	123.20	89.50	1.21

TABLE III—ARTERIAL BLOOD GAS STUDIES AND ALVEOLAR GASES

Pat.	O_2 Content (Vol.%) Rest	O_2 Content (Vol.%) Exerc.	O_2 Satur. (%) Rest	O_2 Satur. (%) Exerc.	CO_2 Content (Vol.%) Rest	CO_2 Content (Vol.%) Exerc.	pH Rest	pH Exerc.	pCO_2 mm. Hg. Alveolar Gases	pO_2 mm. Hg. Alveolar Gases
1. O. D.										
Before Rx	18.87	18.86	97.46	97.92	45.81	45.19	7.44	7.38		
After Rx	15.86	16.02	90.78	91.70	44.95	46.02	7.44	7.41		
2. C. M.										
Before Rx	17.55	18.34	93.20	93.90	45.40	44.19	7.39	7.37	38.75	101.43
After Rx	18.75	18.26	90.14	92.60	47.75	43.70	7.40	7.40	39.40	99.22
3. M. B.										
Before Rx	15.57	16.16	91.27	94.72	51.16	48.63	7.38	7.38	37.31	106.93
After Rx	15.54	16.90	90.30	98.20	51.16	46.50	7.37	7.37	40.93	91.62
4. J. O'N.										
Before Rx	16.51	18.13	90.61	99.51	45.64	42.72	7.39	7.36	34.51	107.45
After Rx	16.14	17.03	94.00	99.18	46.27	43.93	7.40	7.42	33.21	108.37
5. M. H.										
Before Rx	15.63	16.49	92.54	84.18	49.94	49.57	7.37	7.36	49.49	91.31
After Rx	15.92	16.27	95.50	96.60	53.54	53.06	7.43	7.39	40.11	105.70

Side Effects

Side effects, although numerous, were transient, not severe, and no interruption of treatment was necessary in any of the five cases. Slight rounding of the face developed in all. In one, there was mild transient acne. A slight rise in blood pressure was observed in Cases 3 and 4. All had moderate weight gain, probably due to water retention. The determination of blood electrolytes showed no significant changes.

Discussion

Before treatment, the essential clinical findings in all five patients were x-ray film evidence of marked pulmonary involvement, low exercise tolerance, cough, malaise, fatigue, lassitude and weight loss. Ocular involvement was extensive in two and of a moderate degree in one patient. One had uveoparotitis and facial nerve paralysis, probably secondary to it. Skin involvement was not extensive and was limited to the face in two and to the arms in a third. The intradermal sarcoidosis (Nickerson-Kveim) test was positive in four and negative in Case 2. The diagnosis in this patient was based on the clinical findings and mediastinal lymph node biopsy. A negative sarcoidosis intradermal test is encountered occasionally. Although some investigators feel that a positive tuberculin test excludes sarcoidosis, other workers have demonstrated the co-existence of the two diseases in 10 per cent or more of clinical cases, and of greater frequency in autopsy material.[5, 12] Of the two who had positive tuberculin test, one also had positive lepromin test. The lepromin test may be positive in cases with positive tuberculin tests through the mechanism of cross sensitivity.

Pulmonary function studies showed only slight impairment in lung volume measurements compatible with the findings of minimal pulmonary emphysema. The ventilatory reserve was moderately diminished in all, but not down to values indicating severe dyspnea, i.e. 70 per cent or less. None gave evidence of diffusion difficulty or disturbance in acid-balance equilibrium. *It is of interest to note the discrepancy between the x-ray findings, which in some cases were extensive, and the relatively slight impairment of the pulmonary functions.*

A marked suppressive effect of ACTH and cortisone upon the sarcoidosis lesions was observed in all of the five patients treated. Regressions were of various degrees, depending largely on the organs involved and the acuteness of the lesions. In none was the remission complete or equal at all sites of involvement. Objectively, the lesions of the skin, peripheral lymph nodes, parotid gland and eyes were most favorably affected. These lesions regressed early in the course of treatment with no significant residua. Subjectively, a marked improvement in dyspnea, cough and general well being was observed in all. In nine months' follow up after cessation of treatment, no relapse occurred, with the exception of Case 1. Approximately six months after cessation of treatment, this case has a recurrence of infiltrate over the left malar area at the site of the previous lesions.

We have no evidence that the basic, natural course of the disease is altered profoundly or permanently by treatment with these hormones; their suppressive effect may be valuable in reducing the damage to vital organs during the active phase of the disease. From their effect on the objective symptoms in our cases, we feel it is reasonable to assume that systemic administration of ACTH and cortisone accelerates the rate of spontaneous recovery.

Because prolonged systemic treatment with the corticotrophic hormones may cause serious disturbances in electrolyte and endocrine balance, their use should be reserved for patients in whom the sequelae of sarcoidosis may have serious consequences, or they may be used to initiate a more rapid rate of natural reparative process.

CONCLUSIONS

1. Sarcoidosis, when encountered in any of its special forms, should be studied for evidence of pulmonary involvement, as well as for other systemic manifestations.

2. Adrenocorticosteroid therapy, when surrounded by the proper safeguards of complete laboratory controls and careful clinical observations, may be safely used over a period of time of from four to six weeks (possibly longer), to initiate resolution of the clinically active manifestations of sarcoidosis.

3. Pulmonary pathology of sarcoidosis responds more slowly to adrenocorticosteroid therapy, as measured by pulmonary function studies, and to a lesser degree than do skin and other visceral lesions.

RESUMEN

1. La sarcoidosis cuando se encuentra en cualquiera de sus formas especiales debe ser estudiada buscando evidencias de compromiso pulmonar así como de otras localizaciones.

2. La terapéutica adrecorticosteroide cuando se rodea de adecuadas precauciones, de control completo de laboratorio, y de observación clínica conveniente, puede usarse con seguridad por un período de cuatro o seis semanas (quizás más) para iniciar la resolución de las manifestaciones clínicas activas de sarcoidosis.

3. La patología pulmonar de la sarcoidosis responde más lentamente según lo denotan los estudios funcionales pulmonares, y en grado menor que las lesiones cutáneas y viscerales.

RESUME

1. La sarcoidose, quand on l'observe dans toutes ses formes devrait être étudiée aussi bien dans ses manifestations pulmonaires que dans les autres atteintes viscérales.

2. La thérapeutique par l'adrénocorticostéroïde, sous contrôle d'examens de laboratoires complets et d'une observation clinique minutieuse, peut être efficacement utilisée pendant une période de temps variant de quatre

à six semaines (éventuellement plus longtemps) pour amorcer la résolution des manifestations cliniques actives de la sarcoidose.

3. D'après l'étude de la fonction pulmonaire, les lésions pulmonaires de la sarcoidose répondent plus lentement et plus faiblement au traitement adrénocorticostéroïde que les lésions cutanées ou viscérales.

SCHLUSSFOLGERUNGEN

1. Begegnet man dem Sarcoid in irgend einer seiner speziellen Formen, muss man nach Beweismaterial für eine pulmonale Beteiligung suchen ebenso wie nach anderen Organ-Manifestationen.

2. Schliesst die Behandlung mit Adrenocorticosteroiden die gründliche Vorsichtsmassregeln vollständiger Laboratoriumskontrollen und sorgfältiger klinischer Beobachtungen ein, so kann sie vorsichtig über einen Zeitraum von 4-6 Wochen und möglicherweise länger angewandt werden, um die Rückbildung der klinisch aktiven Manifestationen des Sarcoids einzuleiten.

3. Die pulmonalen pathologischen Veränderungen beim Sarcoid sprechen langsamer auf die Adrenocorticosteroid-Behandlung an, wie nach den Lungenfunktionsprüfungen abzuschätzen ist, und auch in geringerem Grade als die Herde an Haut und anderen Organen es tun.

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Pulmonary Emphysema, Cardio-Respiratory Disturbance*

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Pulmonary emphysema, as the term is generally used clinically, refers to an overinflation or distention of the lungs (localized or diffuse), characterized by a relative increase in the amount of air which cannot be blown out with a forced expiration. The residual air capacity plus the vital capacity equals total observed lung capacity (TLC) for the individual, and in pulmonary emphysema the TLC value may be the normal predicted, increased or decreased.[1] Wide individual variations of the total lung capacity have been noted in patients with pulmonary emphysema, in some cases the TLC was increased as much as 40 per cent above the normal predicted, and in other cases decreased more than 65 per cent below the normal predicted. In order to determine the total lung capacity, the residual air, that which remains at the end of a forced expiration, must be measured and added to the vital capacity. The severity of emphysema cannot be evaluated unless the residual air be considered in relation to TLC, for although the residual volume may be less than the predicted, the ratio to TLC may be markedly increased in some cases because vital capacity is greatly reduced. Even when the absolute value of the residual air is markedly increased above the predicted normal, in order to assess accurately the degree of pulmonary emphysema present, this volume must be expressed as a ratio or percentage of total lung capacity. If the residual air occupies 35 to 45 per cent of total lung capacity a moderate, but significant degree of pulmonary emphysema exists, from 45 to 55 per cent an advanced or severe degree of pulmonary emphysema is present and above 55 per cent there is a far advanced or very severe degree of pulmonary emphysema.[2] The normal ratio of residual air is less than 35 per cent of TLC in the 15 to 70 year age group.[3] The residual per cent of total lung capacity presents a reliable consistent reference measurement, and in general the average ratio does not change significantly from the supine to standing or even walking.[4, 5] The functional residual capacity (FRC) does vary significantly from the supine to the standing position because of the shift in the level of the diaphragm which changes the expiratory reserve air, and the activity of exercise further alters the FRC to various degrees.

In emphysema hyperventilation is the compensatory mechanism which attempts to maintain the mean alveolar pO_2 as near the normal level as possible and to blow off CO_2. Hyperventilation may meet the demands at rest if the emphysema is not too severe, but with exercise the hyper-

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ventilation is frequently inadequate to provide sufficient alveolar aeration. The pathological changes in the lung resulting in an increased residual ratio of total lung capacity also cause extensive disturbance in the uniformity of air distribution in the lung with impaired ventilation of many alveoli, and an elevated alveolar nitrogen value above 1.5 per cent after breathing oxygen for seven minutes reflects this disturbance, and in this laboratory preliminary studies indicate the alveolar nitrogen just as reliable and as accurate as the nitrogen curve with a single deep breath of oxygen on the nitrogen meter. In general, severe emphysema produces a mean alveolar pO_2 below the normal level of 100 mm. Hg. at sea level pressure,[1] unless compensatory hyperventilation is adequate to correct for the abnormality. Some alveoli are closer to the outside air and are normally more easily ventilated than others more distal with a relative hypoventilation. In pulmonary emphysema the situation is greatly magnified for these normally less easily ventilated alveoli, so that on ambient breathing many alveoli are very poorly ventilated although still perfused with blood. The use of a slight positive pressure to assist inspiration increases air flow in the poorly ventilated alveoli and improves the arterial blood oxygen saturation because the blood passing through the poorly ventilated alveoli is exposed to a higher oxygen tension with pressure breathing and is therefore more nearly saturated than on ambient breathing. Bronchospasm, a frequent complication in emphysema, impairs still more the disturbance in uniformity of air distribution in the alveoli, especially those farthest removed from the trachea and otherwise less easily ventilated.

Spirogram recordings on the 13½ liter Collins Respirometer provide dynamic quick and accurate records of total vital capacity, the timed vital capacity for three seconds and the maximal breathing capacity.[1] The characteristic features of the breathing curve are easily observed on the spirogram recordings. If the exhalation curve on the spirogram tracing is markedly prolonged, except in asthmatic attacks, a significant degree of pulmonary emphysema is usually present, but the severity cannot be estimated from the spirogram tracings alone. The spirogram tracings in emphysema characteristically reveal a prolonged exhalation time, evidence of air trapping which is apparent after a few deep breaths taken in rapid succession (as during the maximal breathing capacity test), involving rapid voluntary respiratory movements at a high inspiratory level since the lungs are kept filled with more air than normal to decrease breathing resistance as much as possible. If the supine vital capacity is significantly greater than the standing vital capacity, a severe degree of pulmonary insufficiency is indicated. The measurement of vital capacity in two separate steps (as the sum of inspiratory reserve and expiratory reserve) is subject to error from shifts in the level of the diaphragm and is unsatisfactory.

A ventilation factor,[2] that provides a single figure value of the patient's ability to use the chest and lungs as a bellows to aerate the alveoli, has been found most useful, and well correlated with the arterial pCO_2 by direct

tension measurement. The ventilation factor approximates on a percentage basis the efficiency of the lungs as a bellows, and the value is determined from the average of three measurements, all expressed as per cent of the normal predicted, namely: the three second vital capacity, the maximal breathing capacity and the residual air capacity as per cent of total lung capacity. If the ventilation factor at rest is decreased as low as 25 per cent of predicted, dyspnea is usually present.

The arterial blood oxygen saturation varies widely in pulmonary emphysema both at rest and during exercise. Data from 25 cases, all with either a severe or very severe degree of pulmonary emphysema, reveal the

TABLE I
STUDIES ON THE NATURE OF THE ARTERIAL BLOOD OXYGEN UNSATURATION IN PULMONARY EMPHYSEMA

Case No.	Residual % of Total Lung Capacity	Ventilation Factor, %	Arterial Blood Oxygen Saturation, Per Cent				
			Rest Ambient Air	Rest IPPB Air	Step-up Ex. Air	Step-up Ex. 30.0% O_2	Rest 100% O_2 6 Min.
836	67.0	28.8	86.0	91.8	74.8	91.0	98.7
1029	48.7	53.6	92.7	96.0	91.8	91.3	98.9
1030	49.9	49.7	89.9	95.2	93.7	95.2	98.0
1039	47.1	50.6	89.1	93.6	93.2	95.0	98.5
1061	52.6	41.5	93.5	94.4	92.8	94.8	98.4
1066	51.7	42.8	91.1	96.0	88.9	93.0	98.7
1074	50.0	46.9	91.0	93.6	78.4	87.4	98.0
1078	74.8	30.4	94.1	94.0	87.5	92.6	99.0
1084	45.3	66.2	92.5	95.0	88.8	92.1	98.0
1086	56.2	52.8	90.1	95.8	82.7	92.2	98.9
1101	57.9	41.5	93.3	94.5	92.2	92.4	98.8
1102	66.0	34.6	93.7	95.2	89.9	94.4	98.9
1109	53.2	36.3	87.7	93.0	77.8	91.0	100.0
1113	57.7	37.9	87.0	92.2	73.8	87.9	98.4
1119	54.7	36.6	85.4	93.0	86.6	94.0	100.0
1121	51.4	55.8	87.7	93.0	88.5	91.8	95.8
1125	68.7	31.5	87.1	93.2	86.7	92.0	98.1
1129	45.2	40.0	93.5	94.5	92.3	94.3	99.2
1131	70.9	29.1	85.8	91.0	76.1	89.4	98.5
1132	58.8	45.7	89.3	96.8	82.4	94.9	98.9
1134	45.2	73.4	90.4	93.4	87.5	90.6	96.5
1135	45.0	49.5	94.2	96.0	80.0	87.2	99.5
1136	45.9	39.5	94.1	95.8	87.8	92.4	99.2
1138	50.7	48.4	88.3	94.2	83.2	89.0	97.3
1140	46.5	65.4	90.0	97.5	93.0	95.3	100.0
Average	54.4	45.1	90.3	94.3	86.0	92.0	98.6

resting arterial blood saturation decreased in a slight to very marked degree with an average of 90.3 per cent and a range of 94.2 to 85.40 per cent, Table I. The arterial blood oxygen saturation was decreased during step-up exercise in most of the cases of severe emphysema, but in four cases the exercise saturation was slightly higher than the resting, Table I. There was no apparent correlation of the residual per cent of total lung capacity or the ventilation factor per cent of normal with the resting or exercise arterial blood oxygen saturation, Table I. The arterial blood oxygen saturation was significantly increased with intermittent positive pressure breathing (IPPB) on compressed air only (no bronchodilator) as a diagnostic test, the average saturation increase being 4 per cent at rest, and in some cases even up to the normal value of 96 per cent or more. There was only one instance in which the blood saturation was not increased above the resting level with the pressure breathing on air. The improved saturation with pressure breathing on air indicates the presence of poorly ventilated alveoli on ambient air breathing.

Further exploration was made of the nature of the exercise unsaturation. The step-up exercise was repeated with the patient breathing a high oxygen mixture (30.0 per cent oxygen), as this provides an inspiratory pO_2 above 200 mm. Hg. (normal 150 mm. Hg. at sea level on air). If the lowering of the arterial blood oxygen saturation with exercise resulted from a diffusion difficulty, then the high oxygen breathing with the increased inspired pO_2 should restore the blood saturation to the normal level of 97 per cent or more. The pressure breathing at rest on air does not elevate the mean inspired pO_2 a sufficient degree to be a factor in overcoming a diffusion difficulty if present at the pulmonary membrane. Data are presented in Table II from three cases with proven shunts from right to left and IPPB on air did not produce a significant change in the resting arterial blood oxygen saturation in two of the cases so studied. During step-up exercise with a high oxygen breathing mixture in the emphysema cases the arterial blood oxygen saturation was still abnormally low, 95 per cent or less, with an average of only 92 per cent, Table I. These data indicate that during the step-up exercise with the increased cardiac output from the right side of the heart some blood by-passes ventilated alveoli with shunting, a condition which the high oxygen breathing mixture does not correct, see also Table II, where 100 per cent oxygen breathing did not correct the saturation to the normal level of 99 per cent or more in shunts.

The use of two simple tests, intermittent positive pressure breathing on compressed air only at rest and a high oxygen breathing mixture (30 per cent oxygen) with exercise provides very useful information on the nature of the lowering of the arterial blood oxygen in emphysema and fibrosis. A lower saturation occurs at rest because many alveoli are poorly ventilated on ambient breathing, as some alveoli are poorly aerated yet perfused either normally or with a decreased amount of blood, other alveoli are perfused but not aerated (this actually represents a small shunt at the alveolar level) and some alveoli are ventilated but not perfused

with blood. When a marked drop in the exercise arterial blood oxygen saturation occurs as compared to the resting value, the defect is primarily one of shunting blood through nonventilated areas rather than a diffusion difficulty at the pulmonary membrane. The increase in the exercise arterial blood oxygen saturation noted in some cases, comparable to that produced by intermittent positive pressure breathing on air, represents a more uniform alveolar aeration provided by the deeper breathing of exercise. Even with 100 per cent oxygen breathing the normal level (99-100 per cent) was not attained in most of the cases, Table I. A value of 97.0 per cent or less on 100 per cent oxygen indicates extensive shunting, Table II. Even with 100 per cent O_2 breathing during step-up exercise, the arterial blood oxygen saturation was markedly decreased in one case of shunting through a large auricular septal defect with severe pulmonary artery hypertension, case 1055, Table II, indicating that most of the increased cardiac output with the exercise was shunted through the defect, and that the blood passing through the lung on air breathing was essentially normally saturated. The data presented in Table II indicate the shunting in the severe emphysema case with exercise to be of small

TABLE II
DISTURBANCE OF BLOOD GAS EXCHANGE IN SHUNTS

Case Number		221*	854**	1055***	1102
Diagnosis		Large arteriovenous fistulae, left lower lobe	Multiple, small arterio-venous fistulae	Large inter-auricular septal defect, pulmonary artery hypertension	Pulmonary emphysema very severe
Arterial Blood Oxygen Saturation %	Rest, ambient, air	89.0	87.6	85.3	93.7
	Rest, IPPB, air	.....	87.5	84.3	95.2
	Rest, 40% O_2	.....	92.4	86.5	.....
	Rest, 100% O_2	90.6	97.2	94.4	98.9
	Exercise, air	86.0	72.0	54.0	89.9
	Exercise, 30% O_2	.....	.....	.....	94.4
	Exercise, 100% O_2	.....	.....	63.0	.....
Arterial Blood CO_2 cont. Vol. %	Rest, air	39.40	37.65	37.85	54.00
	Exercise, air	38.65	36.00	42.85	52.25
Arterial Blood Tensions Direct Measurement	Rest pCO_2, air	28.7	29.0	35.4	47.1
	Rest pO_2, air	55.4	81.3	67.5	93.1
Minute Ventilation, Exercise L./min./Sq.M./BSA		15.60	17.00	13.10	10.90
Oxygen Uptake, Exercise ml./min./Sq.M./BSA		654	508	264	327

*Studied before and after left lower lobe lobectomy.
**Demonstrated by plastic injection technique of lungs at post mortem.
***Cardiac catheterization.

magnitude as compared to the other cases, but qualitatively similar.

Previous published reports have indicated the inaccuracy of evaluating the carbon dioxide status in patients with very severe degree of pulmonary emphysema,[6] especially when complicated by right heart failure. An elevated CO_2 content indicates inadequate alveolar aeration and represents a warning of the possibility of respiratory acidosis developing during infections or in the presence of a depressed respiration by sedatives, drugs, high oxygen breathing or anesthesia. Drowsiness, stupor, or coma, characteristic symptoms of respiratory acidosis appear to be related more to pH changes than to the absolute level of the CO_2 content or pCO_2. It has been repeatedly observed that a much better correlation exists between the mental status of the patient and pH change, than pO_2, CO_2 content or pCO_2 in the presence of a severe degree of pulmonary emphysema complicated by infection.[6] Respiratory acidosis is prone to develop from oxygen administration in the presence of a severe degree of hypoxia associated with very severe emphysema. The high oxygen breathing decreases the minute ventilation by removing part of the reflex stimulus to the respiratory center from the carotid bodies (the latter are stimulated by a low pO_2). The high oxygen breathing relieves the arterial blood oxygen unsaturation and removes the reflex stimulus from the carotid bodies with a resulting decrease in the total minute ventilation which decreases the CO_2 washout in some cases to a critical level, unless ventilation is supported by mechanical aids (IPPB units or the Drinker type respirator).

The direct determination of the arterial blood pH is necessary to accurately determine the exact status of acidosis or alkalosis in some patients with a severe degree of pulmonary insufficiency.[6] The pCO_2 as calculated[7] from the arterial blood oxygen capacity, pH and CO_2 content has been correlated with the direct determination of the arterial pCO_2 by the Riley bubble method,[8] Figure 1, in 98 cases with a severe or very severe degree of pulmonary emphysema as measured by the residual per cent of total lung capacity and with a ventilation factor less than 60 per cent of normal. An unsatisfactory correlation was noted in general, Figure 1, between the two sets of measurements, and in a majority of the cases, the calculated arterial pCO_2 was too low. However, in some cases it was higher than the pCO_2 obtained by direct tension measurement, which has been found accurate within one to two mm. Hg. In chronic pulmonary disease the calculated arterial pCO_2 does not appear to be a very accurate measurement, and a statistical study of the data on Figure 1 revealed a standard deviation of 7.1 mm. Hg. Since the calculated pCO_2 is inaccurate as compared to direct determination, the calculated pH values would also be an unreliable measurement in patients with severe pulmonary emphysema. The direct determination of the arterial blood pH on a glass electrode does provide an accurate pH measurement regardless of the oxygen capacity, CO_2 content, pCO_2 or CO_2 combining power. A poor correlation of the arterial CO_2 content and the pCO_2 with the pH has been reported previously using direct measurements of

these values in 30 cases of severe pulmonary insufficiency,[6] and the importance of the direct determination of arterial blood pH in the accurate diagnosis of acidosis or alkalosis in the individual case has been emphasized. Although the calculated pCO_2 and pH values are accurate in normal lungs it does not hold that this is necessarily true in patients with marked degrees of pulmonary insufficiency. An arterial puncture of the brachial or femoral artery is usually an easy procedure with the B&D Cournand type needle, and the direct pH measurement can be quickly and accurately performed on the Cambridge glass electrode pH meter.

Patients with severe pulmonary emphysema are unable to increase the pulmonary blood flow corresponding to the degree of exercise given, hence the exercise oxygen uptake is reduced and indirectly indicates the presence of increased pulmonary vascular resistance without the necessity of catheterizing the right heart to measure pulmonary artery pressure and cardiac output. The oxygen uptake was normal in the two cases of arterio-venous fistulae, Table II, very markedly reduced in the large interauricular septal defect with pulmonary artery hypertension and markedly decreased in the very severe cases of pulmonary emphysema. The minute ventilation was increased in all cases, very markedly in the two cases of arterio-venous fistulae. The CO_2 content and pCO_2 (direct measurement) were reduced

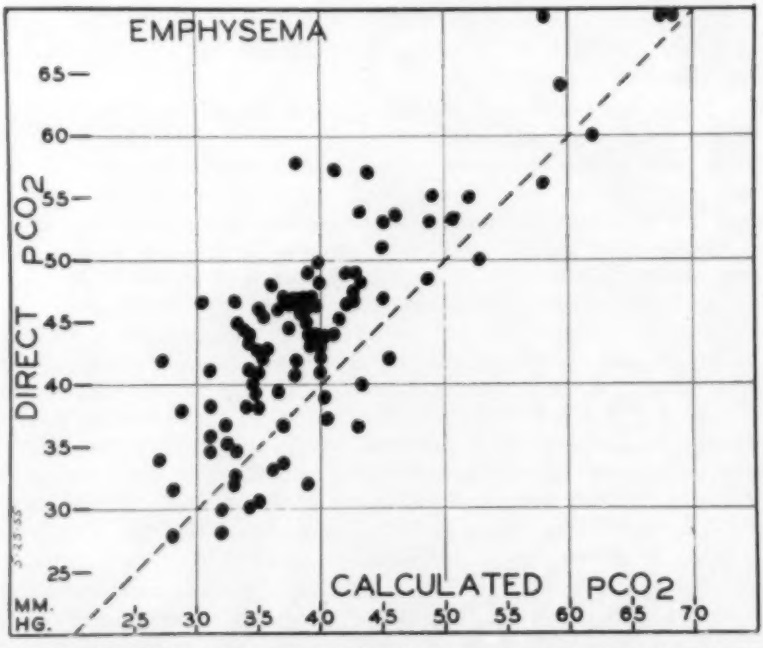

FIGURE 1: Correlation of the calculated pCO_2 (from direct measurements of arterial blood oxygen capacity, CO_2 content and pH[7]) in 98 cases of severe or very severe degrees of pulmonary emphysema with the direct tension measurement of arterial pCO_2 (by the bubble method of Riley.[8]) Residual air was 45 per cent or more of total lung capacity in all cases.

in all cases except the severe emphysema. The exercise CO_2 content as compared to the resting was reduced in all cases except the septal defect, where an increase occurred, indicated very little increase in pulmonary blood flow with exercise and further supported by the very small increase noted in the hemoglobin oxygen saturation during exercise, breathing 100 per cent oxygen. The resting pO_2 tension (direct measurement) was also poorly correlated with the Van Slyke hemoglobin oxygen saturation from oxygen content and capacity in the four cases, a characteristic feature of shunting. The exercise oxygen uptake has been found to be well correlated with the ventilation factor,[2] whereas the per cent of oxygen extracted from the inspired air breathed with exercise frequently shows no significant correlation.[2] Since an adequate minute ventilation and pulmonary blood flow are the two factors necessary to remove from the lung an amount of oxygen corresponding to the exercise given, when the ventilation is adequate and the oxygen uptake reduced, a decreased pulmonary blood flow is indicated. A marked decrease in the exercise oxygen uptake was observed in the case of the congenital heart defect with an interauricular septal defect and pulmonary artery hypertension, Table II, indicating a very marked reduction in the pulmonary blood flow as compared to the normal in exercise, in this case most of the increased output was shunted through the septal defect and this is further indicated by the very low arterial blood oxygen saturation on 100 per cent oxygen during the step-up exercise (63.0 per cent). The inability to increase the pulmonary blood flow during exercise because of increased vascular resistance and lack of expansibility of the pulmonary bed is a very characteristic finding of pulmonary emphysema, and the decreased oxygen uptake is easily demonstrated by the one minute step-up test.

SUMMARY

1. The ratio of the residual air to total lung capacity (TLC) is necessary to determine the severity of pulmonary emphysema, for in some cases the absolute volume of the residual air may be decreased below the predicted normal and yet represent a very high ratio to TLC because of a very marked decrease in vital capacity; and even when the residual air is greatly increased, to accurately assess the severity of the emphysema, the ratio to TLC is necessary. The vital capacity, the timed vital capacity for three seconds and the maximal breathing capacity are reduced in various degrees in emphysema, and bronchospasm is of frequent occurrence. The spirogram tracings in emphysema characteristically reveal a prolonged exhalation time and evidences of air trapping after a few deep breaths in rapid succession.

2. The uniformity of alveolar aeration is impaired in pulmonary emphysema, lowering the mean alveolar pO_2, decreasing the saturation of blood perfusing poorly ventilated alveoli and elevating the arterial pCO_2 because of inadequate alveolar aeration. The oxygen tends to pass across the alveolar-capillary membrane in proportion to the respective pO_2 tension in the individual alveoli.

3. The arterial blood oxygen saturation was decreased below the resting level with exercise in most cases of severe emphysema. The resting saturation when decreased can be increased to normal or near normal or significantly increased in most cases with intermittent positive pressure breathing (IPPB) on compressed air only, indicating the cause as poorly ventilated alveoli. The drop in exercise saturation was not restored to normal with high oxygen breathing (30.0 per cent O_2) during exercise indicating that some blood from the right side of the heart with the increased cardiac output by-passes ventilated alveoli with shunting, rather than a diffusion difficulty at the pulmonary membrane.

4. The use of two simple tests, intermittent positive pressure breathing (IPPB) with compressed air only and a high oxygen breathing mixture (30 per cent O_2) with exercise provide information on the nature of the lowering of the arterial blood oxygen saturation in emphysema and fibrosis and other types of chronic pulmonary disease. Diffusion difficulties are infrequent in chronic pulmonary disease as compared to poorly ventilated alveoli and the perfusion of blood through very poorly or non-ventilated areas.

5. Calculated arterial pCO_2 and pH values appear to be poorly correlated with the direct determination of these measurements in severe chronic pulmonary emphysema. The direct determination of arterial blood pH is necessary to accurately determine the exact status of acidosis in some patients with severe degrees of pulmonary insufficiency. The pH change has been better correlated with the mental status than the level of the CO_2 content or pCO_2 in patients with severe pulmonary insufficiency in respiratory acidosis.

6. The inability to increase the pulmonary blood flow during exercise because of increased vascular resistance and lack of expansibility of the pulmonary vascular bed is a very characteristic finding of severe pulmonary emphysema, especially with cor pulmonale. A reduced exercise oxygen uptake in the presence of an adequate minute ventilation indicates the inability to increase the pulmonary blood flow corresponding to the degree of exercise given, and indirectly is a measure of increased pulmonary vascular resistance.

RESUMEN

1. Para determinar la gravedad del enfisema pulmonar se necesita determinar la relación entre el aire residual y la capacidad pulmonar total (TLC), porque en algunos casos el volumen absoluto del aire residual puede descender debajo de la normal esperada y sin embargo representar una relación muy alta a la TCL a causa de una disminución marcada de la capacidad vital; y aún cuando el aire residual está grandemente aumentado es necesaria su relación con TLC para estimar exactamente la severidad del enfisema.

La capacidad vital, la capacidad vital por tres segundos y la capacidad respiratoria máxima, se reducen en grados diversos en el enfisema y el broncoespasmo es frecuente. Los trazos espirográficos en el enfisema revelan de modo característico un tiempo prolongado de exhalación y evi-

dencias de atrapamiento de aire después de unas cuantas inspiraciones profundas en sucesión rápida.

2. La uniformidad de la aereación alveolar está alterada en el enfisema pulmonar haciendo descender la media alveolar PO_2, decreciendo la saturación de la sangre que pasa por alveolas mal ventilados y elevando el pCO_2 arterial por la aereación alveolar deficiente.

Ex oxígeno tiende a pasar a través de la membrana alveolo-capilar y en proporción de la respectiva tensión de oxígeno (pO_2) en el alveolo individual.

3. La saturación de oxígeno de la sangre arterial ha sido menor que el nivel en reposo, con el ejercicio, en la mayoría de los casos de enfisema severo. Cuando la saturación en reposo ha decrecido puede aumentarse hacia lo normal o cerca de lo normal o aún significantemente aumentarse en la mayoría de los casos mediante la respiración a presión positiva intermitente (IPPB) con sólo aire comprimido lo que indica que la causa es la ventilación deficiente de los alveolos. Ia caída en la saturación de oxígeno en ejercicio no se restauró a lo normal respirando oxígeno (30 por ciento de O_2) durante el ejercicio, lo que indica que alguna sangre del lado derecho del corazón con motivo del aumento del rendimiento cardiaco pasa hacia los alveolos ventilados por intercomunicaciones más bien que indicar una dificultad de la difusión en la membrana pulmonar.

4. El uso de dos pruebas sencillas: la presión positiva intermitente con aire comprimido solo y una alta concentración de oxígeno (30 por ciento O_2) con ejercicio proporciona información sobre la naturaleza del decrecimiento de la saturación de la sangre arterial en enfisema, en fibrosis y en otros tipos de enfermedad pulmonar crónica.

Las dificultades de la difusión no son frecuentes en las enfermedades crónicas pulmonares si se comparan con los alveolos mal ventilados y con la perfusión de sangre a través de áreas muy mal ventiladas o no ventiladas del todo.

5. Los volúmenes calculados de pCO_2 y pH parecen estar mal correlacionados con la determinación directa de estas medidas en el enfisema severo pulmonar crónico. La determinación directa del pH de la sangre arterial es necesaria para determinar con exactitud la acidosis en algunos enfermos en grados severos de insuficiencia pulmonar. El cambio del pH ha sido correlacionado mejor con el estado mental que con el nivel del CO_2 contenido en pCO_2 en enfermos con insuficiencia pulmonar en acidosis respiratoria.

6. La incapacidad para aumentar el flujo pulmonar sanguíneo durante el ejercicio a causa de un aumento de la resistencia vascular y a falta de expansibilidad del lecho vascular pulmonar es un hallazgo muy característico del enfisema pulmonar severo, especialmente en el cor pulmonale. Una reducción del consumo de oxígeno en presencia de una adecuada ventilación por minuto indica la incapacidad para aumentar el influjo sanguíneo pulmonar en correspondencia con el grado de ejercicio e indirectamente es una medida del aumento de la resistencia vascular pulmonar.

RESUME

1. Le rapport du volume pulmonaire à la capacité pulmonaire totale est une mesure nécessaire pour déterminer le degré de l'emphysème pulmonaire. Dans certains cas en effet, le volume résiduel en valeur absolue peut décroitre au-dessous du taux normal, et cependant reprèsenter un très fort pourcentage par rapport à la capacité pulmonaire totale, étant donné l'abaissement très marqué de la capacité vitale; le rapport à la capacité totale pulmonaire est nécessaire pour évaluer d'une façon précise la sévérité de l'emphysème, même lorsque le volume résiduel est augmenté. En effet, la capacité vitale, le volume expiratoire maximum en trois secondes, et la ventilation maximale sont réduites à des degrés variables dans l'emphysème, et le bronchospasme y est fréquent. Les tracés spirographiques dans l'emphysème révèlent d'une façon caractéristique une expiration prolongée, une augmentation du volume pulmonaire fonctionnel lors de quelques inspirations profondes sur un rythme rapide.

2. L'homogénéité de la ventilation alvéolaire est troublée dans l'emphysème pulmonaire, ce qui abaisse la pression moyenne d'oxygène alvéolaire, fait décroitre la saturation du sang qui injecte les alvéoles pauvrement ventilées, et élève la pression du gaz carbonique artériel.

3. La saturation oxygénée du sang artériel à l'effort est abaissée audessous du niveau qu'elle atteint au repos dans la plupart des cas d'emphysème grave. La saturation au repos, lorsqu'elle est abaissée, peut dans la plupart des cas être augmentée jusqu'à atteindre le taux normal ou presque normal, ou être augmentée dans des proportions sensibles par la respiration sous pression positive intermittente d'air comprimé. Ceci démontre bien que la cause de l'affection est la pauvreté de la ventilation alvéolaire. Le chiffre de saturation à l'effort n'est pas ramené à la normale par l'inhalation d'air suroxygéné à 30% pendant l'effort. Ce fait indique que, le débit cardiaque étant augmenté, une partie du sang provenant du coeur droit courcircuite les alvéoles ventilées, plutôt que d'invoquer un trouble de diffusion à travers la membrane alvéolaire.

4. L'emploi de deux tests simples, d'une part la respiration sous pression positive intermittente d'air comprimé, et d'autre part l'inhalation d'air suroxygéné à 30% pendant l'effort, fournissent des informations sur la nature de saturation hémoglobinée du sang artériel dans l'emphysème, la sclérose et d'autres types d'affections pulmonaires chroniques. Les troubles de diffusion sont rares dans les affections pulmonaires chroniques par rapport au défaut de ventilation alvéolaire avec conservation de la perfusion sanguine à travers ces régions très pauvrement ou peu ventilées.

5. Le calcul du pCO_2 et du pH artériels dans l'emphysème chronique sévère a donné des valeurs sensiblement différentes de celles obtenues par mesure directe. La détermination directe du pH du sang artériel est nécessaire pour obtenir avec précision le degré exact d'acidose chez certains malades atteints d'emphysème pulmonaire sévère.

6. L'impossibilité d'augmenter le débit de sang pulmonaire pendant l'effort, à cause de la résistance vasculaire augmentée et du manque d'expansion du lit vasculaire pulmonaire, est une constatation caractéristique de

l'emphysème sévère, et spécialement lorsqu'il est associé au "coeur pulmonaire." Un taux d'oxygène faible à l'effort alors que la ventilation minute est suffisante montre l'incapacité d'accroitre le débit du sang pulmonaire proportionnellement à l'intensité de l'effort; il est un signe indirect de l'augmentation de la résistance vasculaire pulmonaire.

ZUSAMMENFASSUNG

1. Um die Schwere eines Lungen-Emphysems beurteilen zu können ist es nötig das Verhältnis Residual-Luft zur Totalkapazität zu kennen, da in manchen Fällen das absolute Residual-Volumen unter den Sollwert gesenkt sein und dennoch ein höherer Wert, verglichen mit der Totalkapazität, (bedingt durch die sehr vermindete Totalkapazität) dargestellt werden kann. Und selbst, wenn die Residual-Luft stark vermehrt ist, erscheint es notwendig die Grösse der Totalkapazität genauestens zu kennen, um die Schwere des Emphysems beurteilen zu können. In den verschiedenen Graden des Lungen-Emphysems und häufig auch bei Bronchialspasmus ist der Atemgrenzwert, die Vitalkapazität und der für drei sekunden der Vitalkapazität-Zeit auszustossende Anteil der Vitalkapazität vermindert. Das Spirogramm zeigt beim Emphysem eine verlängerte Exspirationszeit und Anzeichen von intrapulmonaler Luftaufstauung nach einigen tiefen Atemzügen in schneller Reihenfolge.

2. Die gleichmässige alveolare Belüftung ist beim Lungenemphysem unzureichend, so dass der mittlere alveolare Sauerstoffdruck vermindert wird, die Sättigung des Blutes, das die mangelhaft belüftete Alveolen umströmt, herabgesetzt, und die arterielle CO_2-Spannung daher heraufgesetzt wird. Die Menge des Sauerstoffes, der die alveolo-kapillare Membran passiert, ist abhängig vom entsprechenden O_2-Druck der einzelnen Alveolen.

3. In den meisten Fällen von schwereren Lungen-Emphysem war die arterielle O_2-Sättigung bei Belastung unter dem Ruhewert abgesunken. Wenn die Sättigung in Ruhe vermindert ist, kann sie bei den meisten Fällen durch intermittierende Überdruckatmung mit Luft allein bis zum Normalwert oder bis zum annähernden Normalwert oder zum mindesten deutlich gesteigert werden, womit als Ursache unzureichend belüftete Alveolen erkannt wurde. Durch Atmen von 30% Sauerstoff unter Arbeit liess sich eine bei Belastung verminderte Sauerstoffsättigung nicht normalisieren, was darauf hinweist, dass bei dem vergrösserten Herzminutenvolumen einiges Blut kurzgeschlossen wird, ohne belüftete Alveolen zu passieren, während eine Erschwerung der Diffusion an der Lungenmembran weniger wahrscheinlich ist.

4. Die Benutzung zweier einfacher Tests, nämlich der intermittierenden Überdruckatmung mit komprimierter Luft und der Atmung von 30% Sauerstoff unter Belastung, gibt Hinweise auf die Ursache der Verminderung der arteriellen Sauerstoffsättigung beim Emphysem, bei der Fibrose und bei anderen Arten von chronischen Lungenerkrankungen. Diffusionsstörungen sind bei Lungenkrankheiten weniger häufig als ungleichmässige Belüftung und Durchströmung nicht ventilierter Bezirke.

5. Die berechneten arteriellen CO_2-Spannungs und p_u-Werte scheinen

nur eine geringe Übereinstimmung mit den direkt bestimmten Werten bei schwerem chronischem Lungenemphysem zu haben. Die direkte Bestimmung des arteriellen p_H ist notwendig, um den Grad der Acidose bei manchen Patienten mit respiratorischer Insuffizienz zu beurteilen. Die Veränderung des p_H steht in einem besseren Verhältnis zum Bewusstseinszustand als die Höhe des CO_2-Gehaltes bwz. der CO_2-Spannung bei Patienten mit respiratorischer Insuffizienz und respiratorischer Acidose.

6. Die Unfähigkeit, den Lungendurchfluss bei Belastung wegen des vermehrten Gefässwiderstandes zu erhöhen und der Mangel an Erweiterungsfähigkeit des pulmonalen Strombettes ist ein sehr charakteristischer Befund beim schweren Lungenemphysem, besonders dann, wenn es mit Cor pulmonale einhergeht. Eine verminderte Sauerstoffaufnahme unter Belastung bei Vorhandensein eines ausreichenden Atemminutenvolumens weist auf die Unfähigkeit, den Lungendurchfluss entsprechend der Belastung zu vermehren, hin und ist ein indirektes Mass für einen vermehrten Lungengefässwiderstand.

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The Selection of Cases of Coronary Heart Disease Suitable for Surgical Treatment*

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In the presence of occlusive disease of the coronary arteries the blood supply to the myocardium can be significantly improved by modern surgical techniques. The object of surgery is to create anastomatic communications between the myocardial and extracardiac blood vessels. In experimental animals the success of any revascularization procedure can be demonstrated objectively and conclusively by the coronary artery ligation-mortality-infarct method of Beck,[1] and the Mautz-Gregg[2] backflow method. This plan of investigation has been pursued in our own animal laboratory, and we have become convinced of the validity of the basic principles underlying the surgical treatment of coronary artery disease.

Of course, the results of animal experimentation cannot be directly translated to humans, because of the known species differences in anatomy and pathology of the coronary arterial system, and because of the added important factor of the psyche in man. Unfortunately, in patients the efficacy of a revascularization procedure cannot be demonstrated objectively, and therefore must be evaluated subjectively on the basis of: 1. amelioration of symptoms, 2. ability to return to work, and 3. length of survival. Because of the known wide variability and unpredictability of the course of coronary artery disease, such a method evaluation leaves much to be desired. The lack of objective proof that the myocardium can be revascularized is probably the chief reason for the skepticism with which in the past, a considerable segment of the medical profession has viewed the surgical treatment of coronary artery disease. Despite the fact that Beck introduced his first operation as long ago as 1932, the total experience in this field is comparatively small. The final judgment upon these procedures must wait upon the accumulation of a large number of cases assembled from various clinics, together with a long term controlled follow-up study. We therefore thought it worth-while to report briefly our experience with 32 cases over the past five years with particular reference to the criteria we have formulated for the selection of cases of coronary heart disease suitable for surgery.

We have performed several types of operations, including the Beck I Operation,[1,3] the Beck II[4] Operation (aortic coronary sinus anastomosis and partial occlusion of the coronary sinus where it enters the right auricle), the Vineberg Operation,[5] Omentopexy,[6] and combinations of

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these operations. Our experience is chiefly with the Beck I Operation, which consists of abrasion of the epicardium and parietal pericardium, application of powdered asbestos to these surfaces, partial occlusion of the coronary sinus at its entrance to the right auricle, and grafting of parietal pericardium and mediastinal fat to the surface of the heart.

The average age of our 32 operative cases was 48 years with a range from 32 to 64 years. Twenty-nine of the cases were men and three were women. There were three operative deaths, of which two occurred during the Beck II Operation, and one during combined Poudrage and Vineberg Operation. We had no deaths during the Beck I Operation. Of the remaining patients, 25 (88.3 per cent), have obtained excellent to good results, that is, they have experienced a marked reduction in the frequency and severity of anginal attacks and all were able to resume their usual mode of living. Two patients have had fair results, that is, diminution in the frequency and severity of anginal attacks, but they have been unable to resume their usual occupations. Two had poor results postoperatively. One died two years after the Vineberg Operation. The other has had several attacks of myocardial infarction following the Beck II procedure in which thrombosis of the graft occurred.

Selection of Cases for Surgery

As an aid to the selection of potential candidates for surgery the status of a patient with coronary artery disease may be classified according to the following categories:

1. *Asymptomatic:* In this group are those who have suffered a myocardial infarction in the past but who are not now subject to angina pectoris. Apparently they have developed sufficient collateral circulation to maintain adequate myocardial blood flow. Surgery is not performed for this group. It may not be required, and it would be impossible to prove any benefit in a patient who had been asymptomatic before operation. In the future it may be shown that prophylactic surgery may be of value for this type of case.

2. *Progressive:* These individuals run a rapid downhill course with severe symptomatology. The development of collateral circulation has not kept pace with the advancing disease. In this group surgery is dangerous since the patient may not have developed sufficient collateral circulation to carry him through the trauma of the operation.

3. *Stabilized:* These are patients with the anginal syndrome, with or without previous overt myocardial infarction. The anginal attacks are stabilized with regard to frequency and severity. However, there is insufficient coronary blood flow to maintain adequate circulation for the demands of ordinary living. This is the group for which surgery is performed.

4. *Far Advanced:* Patients in this category have disease of their coronary arteries of such a degree that there is widespread myocardial fibrosis. The heart is enlarged and cardiac insufficiency is often present. Surgical treatment cannot be expected to be of any benefit in these patients since

the myocardial changes are irreversible. Moreover, it must be realized that the operation is not expected to prevent advance of the disease in the coronary arteries, and in the presence of extensive disease surgery will be of no avail.

Thus, for the present, surgery in general is limited to patients in Group III. In actual practice the majority of cases of coronary heart disease fall into this class. In the more specific selection of patients for surgery the following considerations arise, with special reservations for the Beck II procedure and combined operations.

Age. Most of the revascularization procedures can be performed at any age. In this connection physiological age is a more important consideration than chronological age. Our oldest patient was 64, and he obtained an excellent result. Young patients with coronary artery disease usually run a more malignant course than older patients and, therefore, are probably less favorable risks. Two of our three operative deaths were in the younger age group.

Sex. Sex is not a determining factor in the selection of patients for this type of cardiac surgery. Only three of our 31 cases were women, but, of course, the disease is much less prevalent in this sex.

Family History. A history of severe, rapidly progressive coronary heart disease, with death at an early age in other members of the patient's family, does not contraindicate surgery. In fact, it is possible this may prove to be an important indication for the operation on a prophylactic basis.

Angina Pectoris. The presence of the anginal syndrome at this time is considered to be a prerequisite for performance of a revascularization procedure. The angina of effort must be stabilized with respect to frequency and severity of attacks. A progressive increase in symptoms suggests advancing disease and contraindicates surgery, at least temporarily. Angina pectoris that has been static and then suddenly increases in frequency and severity is a warning sign of impending infarction. Surgery at this time is exceedingly dangerous and may prove fatal. The occurrence of status anginosus, however, does not necessarily imply a hopeless prognosis because many cases improve with proper medical management and may then be included in the stabilized group. Status anginosus which does not respond to medical treatment warrants a grave prognosis and contraindicates surgery.

Angina decubitus merits special consideration. In some cases it may be due to heart failure and may respond to appropriate therapy. If the patient then has stabilized angina of effort surgery is indicated. Failure to obtain relief from angina decubitus following medical therapy indicates severe coronary artery disease or impending infarction and surgery should not be advised.

Myocardial Infarction. Following myocardial infarction surgery is not advocated until after a suitable time interval, arbitrarily fixed at six months. The reason for this delay is: first, that the patient must develop

sufficient collateral circulation to carry him through the operation, and, second, in some cases the development of intercoronaries may be so adequate that operation may prove unnecessary. It is important to attempt to assess the degree of myocardial damage which follows coronary occlusion. The absolute number of infarcts is not a good guide since one large infarct may cause more widespread damage than multiple small infarcts. The electrocardiogram by itself does not always reliably measure the size of an infarct, but it must be correlated with the clinical findings of the individual case. A better estimate of extent of damage may be derived from a consideration of heart size, presence of congestive heart failure, development of ventricular aneurysm, and other clinical signs and symptoms.

Blood Pressure. Hypertension, without evidence of involvement of other vital organs, does not contraindicate surgery. Hypertension that is complicated by widespread arterial damage, or severe grades of hypertension is a definite contraindication to surgery.

Heart Size. A slight degree of cardiac enlargement is acceptable in a candidate for surgery. However, moderate or marked cardiac enlargement in arteriosclerotic heart disease represents an advanced degree of myocardial degeneration. Revascularization under these circumstances cannot be expected to produce any significant improvement in cardiac function.

Congestive Heart Failure. Heart failure during the acute stage of myocardial infarction, if transient and promptly responsive to treatment, does not constitute a permanent contraindication to revascularization procedures. However, if the failure is persistent, surgery is contraindicated because irreversible myocardial degeneration is probably present.

Aortic Stenosis. In patients with aortic stenosis it is frequently difficult, if not impossible, to assess the degree to which coronary artery disease may contribute to the anginal syndrome. It is doubtful whether those cases of the anginal syndrome secondary to aortic stenosis alone, in the absence of coronary artery disease, would benefit from the operation. Furthermore, operations of any type are notoriously hazardous in the presence of aortic stenosis. Therefore, for the present, we consider aortic stenosis a contraindication to the revascularization procedure.

Disturbances in Rhythm and Conduction. Surgery is considered hazardous in the presence of arrhythmias. Paroxysmal auricular tachycardia, auricular flutter and fibrillation are frequently associated with an advanced degree of myocardial damage. Moreover, during anesthesia they are unpredictable in their response to drugs. High degrees of A-V block and complete heart block contraindicate surgery because of the danger of ventricular standstill or ventricular fibrillation. Bundle branch block is not a contraindication to surgery. Two patients in our series had right bundle branch block and both obtained good results. Pre-existing left bundle branch block does not contraindicate the operation. However, it should be emphasized that the sudden development of left bundle branch

block during anesthesia or surgery is a grave omen and has been observed to precede ventricular fibrillation and death. One of the operative deaths in our series followed development of left bundle branch block. Beck[7] reported six similar cases. Why this should happen is not clear, but this experience indicates that if left bundle branch block appears during induction of anesthesia or during surgery, the procedure should be terminated immediately.

Diabetes. None of our patients had diabetes. However, we do not consider this condition a contraindication to surgery. As a matter of fact, it may prove to be one of the important indications for revascularization because of its frequent association with arteriosclerotic heart disease.

Obesity. Patients who are markedly overweight withstand the procedure poorly and a weight reducing regimen should be insisted upon before surgery is undertaken.

Psychological Factors. Care must be taken to exclude from consideration those patients who have psychoneurotic symptoms simulating angina pectoris. On the other hand, in true angina pectoris psychic factors play an important role. If a psychic disorder is present and proper psychotherapy is instituted the patient may improve to such an extent that operation may prove unnecessary, or the status of his anginal syndrome may stabilize, permitting surgery to be performed. Patients with angima pectoris who have a psychic disorder which is not treated preoperatively may show no improvement after surgery. In the ordinary case, the cardiologist should be able to evaluate properly the psychic stability of his patient. In more complex cases, the aid of a psychiatric consultant may be required. Preferably, the psychiatrist should be one who has had some training in cardiology.

Although we advise the operation confidently when it is indicated, we do not insist upon surgery in a reluctant patient.

Associated Conditions. Associated serious medical disorders such as: advanced generalized arteriosclerosis, renal insufficiency, severe liver disease or chronic cor pulmonale obviously contraindicate cardiac surgery.

The above criteria apply in a general way to all revascularization procedures. They may be modified to meet the requirements of the surgical technique of the various operations.

The Beck II Operation is a much more formidable undertaking than the Beck I Operation. The technique is more difficult. The operative time is much longer, and two stages are required for its completion. Because of the nature of the operation, that is, the insertion of a vascular graft between aorta and coronary sinus, the criteria for this selection of patients must be much more stringent. There must be no hypertension since an increased pressure in the aorta might cause the graft to "blow out." Excessive hypertension also tends to cause hemorrhage and narrowing of the coronary venous system. Arteriosclerosis of the aorta is also a contraindication since it might interfere with union of the graft. Evidence of cardiac enlargement and congestive failure of any degree are absolute

TABLE I
COMPARISON OF PREOPERATIVE AND POSTOPERATIVE DISABILITY WITH RESULT OF VARIOUS SURGICAL PROCEDURES

Beck I	Age	Sex	Preoperative		Postoperative		Results	Remarks
			Employment	Angina	Employment	Angina		
1. A. A.	38	M	Restricted	2 blocks	Restricted	2 blocks	Poor	Repeat angina with several infarctions postoperatively
2. W. C.	44	M	Discontinued	2-3 blocks	Restricted	Occasional	Good	
3. M. C.	53	F	Restricted	"moderate"	Returned	None	Excellent	
4. N. R.	40	M	Restricted	½ block	Returned	None	Excellent	
5. J. K.	43	M	Restricted	"moderate"	Returned	None	Excellent	
6. H. G.	48	M	Discontinued	"severe"	Returned	Minimal	Excellent	
7. A. H.	32	M	Discontinued	2 blocks	Returned	None	Excellent	
8. F. A.	64	M	Discontinued	"moderate"	Returned	None	Excellent	
9. G. J.	53	F	Discontinued	2-3 blocks	Returned	None	Excellent	
10. W. C.	41	M	Discontinued	2 blocks	Returned	None	Excellent	
11. J. T.	39	M	Restricted	½ block	Returned	None	Excellent	
12. J. C.	45	M	Restricted	5 blocks	Returned	None	Excellent	
13. R. A.	34	M	Restricted	2 blocks	Returned	None	Excellent	
14. T. E.	41	M	Restricted	1½ blocks	Returned	None	Excellent	
15. J. B.	54	M	Restricted	½ block	Returned	None	Excellent	
16. S. S.	50	M	Discontinued	½ block	Returned	None	Excellent	
17. V. C.	57	M	Discontinued	½ block	Returned	None	Excellent	
18. D. M.	44	M	Restricted	2 blocks	Returned	None	Excellent	

Beck II	Age	Sex	Preoperative Employment	Preoperative Angina	Postoperative Employment	Postoperative Angina	Results	Remarks
1. J. C.	43	M	Discontinued	2 blocks	Returned	None	Excellent	
2. W. K.	39	M	Continued	minimal	.....	.....	.....	Expired immediately after surgery
3. W. L.	35	M	Continued	2 blocks	.....	.....	.....	"Blow out" of vascular graft on 13th P.O. day. Expired
4. L. O.	56	M	Discontinued	½ block	Returned	None	Excellent	
5. J. T.	39	M	Discontinued	2 blocks	Returned	None	Excellent	
1st Stage Beck II								
1. W. S.	53	M	Discontinued	½ block	Returned	Minimal	Excellent	
2. T. W.	38	M	Discontinued	2 blocks	Returned	None	Excellent	
Poudrage plus Omentopexy								
1. W. K.	45	M	Discontinued	½ block	Returned	None	Excellent	
2. J. K.	41	M	Restricted	2 blocks	Restricted	3-5 blocks	Fair	
3. B. M.	58	M	Discontinued	2 blocks	Restricted	Occasional	Fair	
Poudrage plus Vineberg								
1. E. C.	55	F	Discontinued	"severe"	Returned	None	Excellent	
2. J. L.	44	M	Discontinued	3 blocks	Returned	None	Excellent	
3. D. C.	54	M	Discontinued	½ block	.....	.....	.....	Patient expired on operating table
Vineberg								
S. F.	55		Discontinued	½ block	Discontinued	½ block	Poor	No relief from surgery. Expired 1½ years later

contraindications. This operation is limited to patients under the age of 50 years.

Combined operative procedures also call for special limitations, since the more extensive the surgery the better general condition of the patient is required.

SUMMARY AND CONCLUSIONS

1. Revascularization of the heart in the presence of coronary artery disease is a feasible procedure.

2. The validity of this premise has been demonstrated in the experimental animal by objective tests, and in the human patient by subjective results.

3. Our experience with 32 cases is briefly summarized.

4. We have done several types of operations. Our present preference is for the Beck I procedure.

5. Based on our experience and the experience of others, and on theoretical considerations, indications and contraindications for revascularization procedures have been formulated.

6. For the present, the indications are limited, but it is hoped that in the future a greater number of cases will be considered proper candidates for surgery.

RESUMEN

1. La revascularización del corazón ante la enfermedad coronaria, es un procedimiento practicable.

2. La validez de este aserto se ha demostrado experimentalmente en los animales por pruebas objetivas y en el enfermo humano por los resultados subjetivos.

3. Se resume nuestra experiencia en 32 casos.

4. Hemos hecho varios tipos de operaciones. Al presente preferimos la operación de Beck.

5. Basándonos en nuestra experiencia y en la de otros, así como en consideraciones teóricas, se han formulado las indicaciones y contraindicaciones para la revascularización.

6. Por ahora, las indicaciones son limitadas pero es de esperar se que en el futuro se considere un número mayor de casos como candidatos adecuados para la cirugía.

RESUME

1. La revascularisation du coeur lors d'une atteinte de l'artère coronaire est un procédé réalisable.

2. La légitimité de ce procédé a été démontrée par des tests objectifs sur l'animal, et chez l'homme par des résultats subjectifs.

3. Les auteurs résument brièvement leur expérience de 32 cas.

4. Les auteurs ont pratiqué plusieurs types d'opération. Leur préférence actuelle va à la première méthode de Beck.

5. Les auteurs formulent les indications et contre-indications des procédés de revascularisation, basées sur leur expérience et celle des autres, et sur des considérations théoriques.

6. En ce moment les indications sont limitées, mais les auteurs espèrent qu'à l'avenir un plus grand nombre de cas seront considérés comme propres à l'intervention.

ZUSAMMENFASSUNG

1. Die Revascularisierung des Herzens bei Vorliegen einer Coronararterien-Erkrankung ist eine durchführbare Massnahme.

2. Die Stichhaltigkeit dieser Prämisse ist beim Versuchstier durch objektive Teste nachgewiesen und beim menschlichen Patienten durch subjektive Ergebnisse.

3. Unsere Erfahrungen an 32 Fällen werden kurz zusammengefasst.

4. Wir haben verschiedene Operationstypen durchgeführt. Was wir gegenwärtig vorziehen, ist das Vorgehen nach Beck I.

5. Basierend auf unserer Erfahrung und der Erfahrung von anderen und auf theoretischen Betrachtungen werden die Indikationen und Kontra-Indikationen für die Verfahren der Revascularisierung formuliert.

6. Einstweilen sind die Indikationen begrenzt, aber es ist zu hoffen, dass in Zukunft eine grössere Zahl von Fällen als geeignete Anwärter zur Operation angesehen werden.

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The Pleural Form of Primary Cancer of the Lung*

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Primary cancer of the lung in its usual anatomical manifestations assumes different formal aspects on which clinical characteristics of its progress and development largely depend.

In this regard those definitions which exclusively refer to anatomic and macroscopic features that characterize the complete clinical picture of the disease have bearing, quite apart from the cellular structure of the newly formed tissues.

It is our intention to examine hereafter a particular anatomical type of primary cancer of the lung, which some researchers have not taken into consideration, but which in our opinion possesses in reality sufficient characteristics of its own to assume special position within the general picture of this disease. We mean by this the so-called pleural form of primary cancer of the lung.

This special name is explicitly mentioned in the classifications of P. Verga,[1] of Roussy and Huguenin,[2] of Olmer and Coll.,[3] of Liberti and Stella,[4] of Eizaguirre:[5] and it is applied to those particular forms of primary cancer of the lung, which rather than affecting the deeper parenchyma, prevalently acquire a surface development, spreading extensively over the pleura.

It is well known that during the development of primary cancer of the lung, affection of the serosa is a frequent event which is capable of assuming different features, such as formation of pleural effusion; diffuse or limited symphisis or thickening without any true tumorous propagation; localized appearances of bysmas and neoplastic masses; metastatizations in the form of waxen drops or plaques.

These are different aspects which are in each case to be explained by different stages of development which mark the general course of the disease.

The term *pleural form of primary cancer of the lung* is, however, intended to give prominence to those forms where the manifestation of heteroplastic tissues on the pleura is preponderant and almost exclusive, and where the affection of pulmonary parenchyma is absolutely marginal.

The precise definition of these forms must necessarily rest, therefore, not on the external aspects of the process alone but also on data of an histological nature.

In the observations which have been made by various researchers, even those where a fair number of cases are involved, it can be noted that the clinical picture does not occur with particular frequency and that as compared with the most common forms of hilar infiltrations, either the mas-

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sive or large nodular type, the cases where pleural affection is involved, always represent an extremely small group. In fact in the case histories of Verga and Botteri (op. cit.) they appear in three of 30 cases, in five out of a 100 in those of Liberti and Stella (op. cit.), in four out of 170 in the studies of Sival.[6]

In our studies, out of 82 cases of primary cancer of the lung, on which we have complete clinical and histological documentation, five presented neoplastic affections of a pleural nature. In reality in only four of them have the clinical and radiological data been supported by post-mortem examination and histological tests. In Case I in the table the patient died at home, two days after having left our institute by his own wish, our diagnostic conclusions are the result of a pleuroscopic examination that permitted direct visual examination of the pleura, which was uniformly invaded by large neoplastic lumps. Further deductions were made as a result of biopsy which made it possible to recognize bysmas and festoons of atypical epithelial elements, of a cylindric and cubic type, with a tendency to range themselves in several rows (Figures 1 and 2).

The individual course of each of the cases which form part of our collection prompts us to give particular consideration to three points which respectively concern the clinical and anatomical course of the disease and its histological characteristics.

Table I summarizes some of the *clinical data* of greatest importance:

TABLE I

Cases	Age in Years	Duration Clinical Course Months	Temp. Fever	Thoracic Pain	Pleural Effusion and its Nature
I : M	62	11	subfebrile initially	++	Abundant—hemorrhagic
II : W	56	6		++	Abundant—simple exudative
III : M	68	9		++	Abundant—hemorrhagic
IV : W	55	10	subfebrile with occasional recurrences	++	
V : M	43	8	subfebrile with occasional recurrences	++	Sacculated—simple exudative

The subjective symptomatology is largely dominated by the affection of the pleura, both when this is in the form of a pachypleuritis syndrome, without the formation of effusion (Case IV in our case histories) and when there is an exudative reaction, of a sero-fibrinous and sero-hemorrhagic type, the quantity of which is always considerable and re-forms readily. The latter type is the more frequent.

In the subjective and functional symptomatology which is usually connected with neoplastic pneumopathy, from the beginning thoracic pain and dyspnea are the phenomena of most importance: Usually there is no cough, when present it is slight and transitory, there is no abundant expectoration or hemoptysis.

FIGURE 1 (CASE I): Chest x-ray film (July 7th, 1953), after emptying the pleural effusion: considerable thickening of the pleural surface at the left side over collapsed lung.

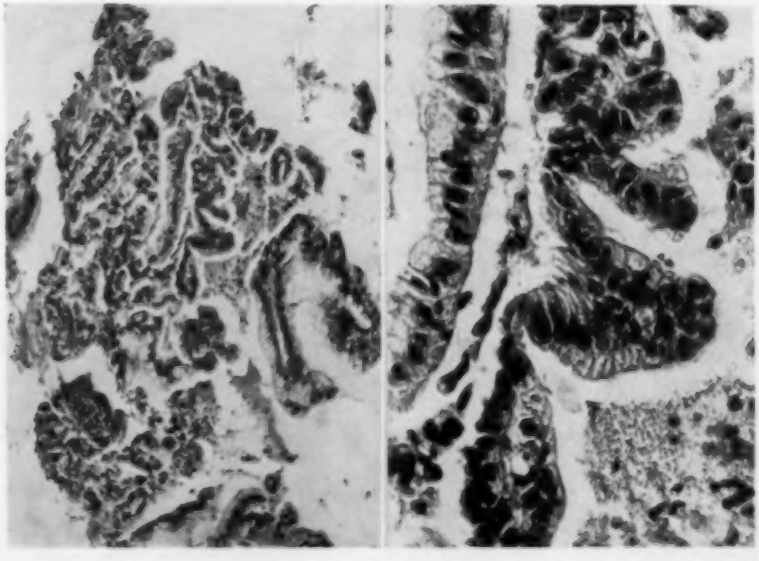

FIGURE 2 (CASE I): Biopsy fragment: neoplastic tissue constituted by epithelial elements of the cylindric type.

Modification of the temperature curve, in the cases studied by us, seems to have no particular trend. In the cases in question there were alterations of a febrile nature only in the initial phases (Case I), in some cases fever occurred from time to time, during the whole clinical course of the disease (Cases IV and V), while in other patients (Cases II and III) there were no febrile reactions during the whole course of the disease.

Thoracic pain, incessant, unremitting and refractory to analgesic action of any kind, are from the beginning localized in the costal area, and radiate in a strip along the thoracic wall and towards the shoulders.

Dyspnea, which is initially connected with physical efforts and particular bodily functions, is considerable from the beginning of the disease. Dell'Acqua[7] notes that it appears to have no true connection with extent of the exudative reaction and is caused, more than by any other factor, by the limitation of movements of the thoracic wall, rendered rigid by the spread of neoplastic tissue on the surface of the pleura.

The entire course of the disease, from appearance of the first clinical data, has in the cases studied by us been from six to 11 months, with an average duration of little more than eight months. This corresponds approximately to figures given by many researchers with regard to primary cancer of the lung: Verga and Botteri (op. cit.) : six months; Grissel and Knox[8]: seven and one-half months; King[9]: nine and one-third months; Liberti and Stella (op. cit.) : seven and one-third months.

Table II summarizes the principal *data of anatomical nature*:

TABLE II

	Side	Affection of the pleura	Pulmonary affection	Metastasis	Histological Type
I	Left	Costal pleura	——	——	Cylindrical cells
II	Right (Fig. 3)	Costal, interlobar and diaphragmatic pleura	Some subpleural bysmas	Lymph-glands liver-kidneys suprarenals	Small undetermined cells
III	Left (Fig. 4)	Costal, mediastinic and diaphragmatic pleura	Bysmas on the hilum with peribronchial location	Lymph-glands liver	Adeno-carcinoma mucigenous (Fig. 5)
IV	Left	Costal and diaphragmatic pleura	Parahilar block extending to lower lobe	Right lung-liver	Cylindrical cells trabecular papillar (Fig. 6)
V	Right	Costal, interlobar and mediastinic pleura	Some subpleural bysmas	Lymph-glands	Small undetermined cells (Fig. 7)

Leaving aside Case I, which was not anatomically checked, but which was clearly defined from an histological aspect as result of biopsy (Fig. 2), in all our other cases, there has always been evidence of a clear lack of proportion between the affection of the pulmonary parenchyma by the neoplastic mass and its development on the surface of the pleura.

In the lung, small or on occasion larger blocks of neoplastic tissue have been found in the vicinity of the hilum, in the form of plaques and bysmas located between the broncho-vascular formations and sometimes spreading

towards the upper or lower lobes. In general there has been no evidence of extensive proliferation inside the diameter of the large bronchial sections. Often, at this level, however, the mucosa was found to be clearly infiltrated. In one of our subjects (Case III) the neoplastic tissue showed immediately after the parahilar block, a clear tendency to spread to the peribronchial area, wrapping itself muff-like around the branches of the segmentary bronchial tubes.

In some other cases (II and V) large inter-parenchymal blocks were found only on the costal side, and appeared to be due to the direct spread of the effusion on the pleura towards the lung.

This parenchymal affection is always relatively moderate and in comparison, the spread of the tumor on the surface of the pleura has always been found to be extensive. Only in one case (IV) this occurred in the form of a large effusion which sealed together the visceral and parietal pleura and then wrapped itself around the whole lung. This was particularly true on the costal and mediastinic areas. In other cases the two leaves of the pleura remained separated, even though partially. This caused the creation of a cavity, which in some cases was large in size (Cases II and III) and in some smaller (Case V). This cavity was lined by thick neoplastic layers—up to a thickness of one centimeter—which formed on the visceral and parietal pleurae.

The possibility that the neoplastic invasion could proceed towards the inter-lobar pleura (Cases II and V), towards the mediastinal pleura (Cases III and V), and towards the diaphragmatic areas (Cases II, III and IV), was frequently evidenced in our cases, and had the usual characteristics.

Metastatic affection of the lymph nodes of the hilum, of the lung, and of

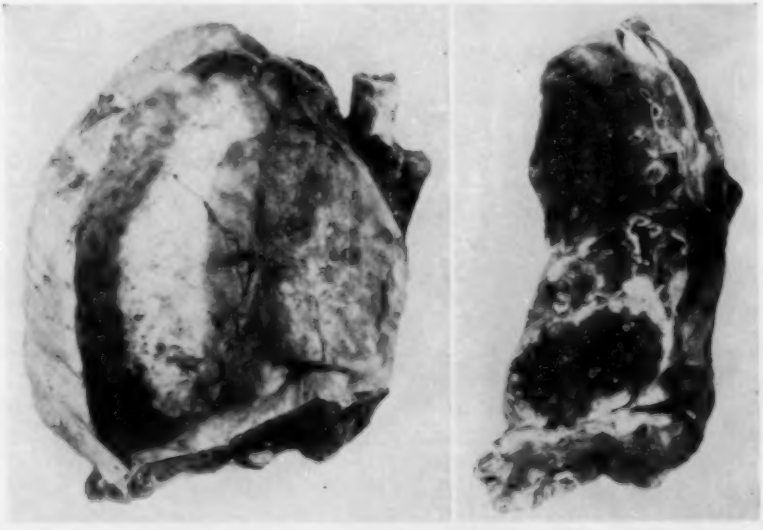

FIGURE 3 (CASE II): Right pleural space and collapsed lung stump; spreading of the neoplastic tissue over the surface of the costal pleura and over the interlobar and diaphragmatic surfaces.

the mediastinal lymph nodes, although often formed by bysmas and festoons of varying size, never assumed the character of a massive invasion. In some cases indeed (IV) there was no macroscopic evidence of an involvement worthy of note.

In three cases—out of the four on which anatomical studies were made —there was found to be a metastatic focus of other organs: liver, three times (Cases II, III, IV), kidneys and suprarenals, once (Case II), contra-

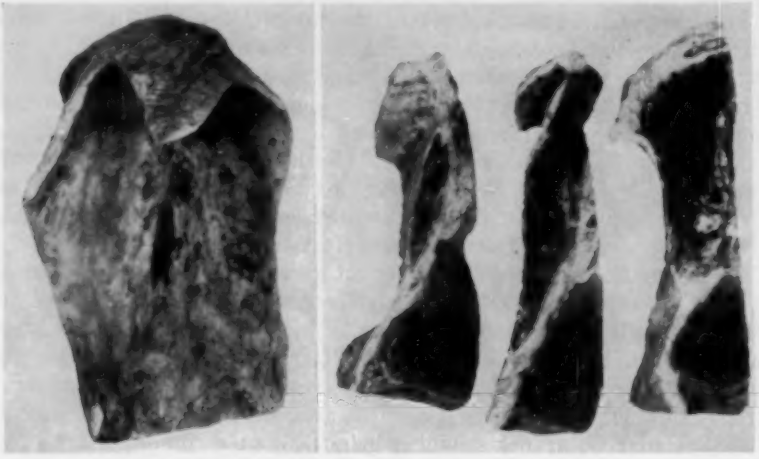

FIGURE 4 (CASE III): Left pleural space and collapsed lung stump: spreading of the neoplastic tissue over the surface of the costal and mediastinal pleura.

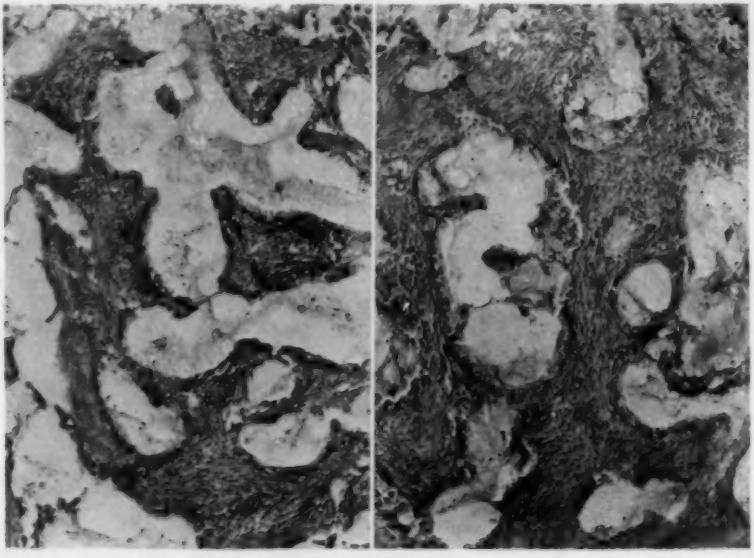

FIGURE 5 (CASE III): Histological fragment of the pleural surface: adeno-carcinomatous mucigen pattern on a thick collagen tissue.

lateral lung (Case IV), once.

With reference to the cases studied by us, Table II gives the histological appearance of the neoplasm. In the first place it is clearly noticeable that the pleural form of primary cancer of the lung has no predilection for any particular histological type. For this reason the cell structure of the substratum may be formed by small undetermined cells, or by cylindrical-polymorphous types, and indeed, by adeno-carcinomatose structures of a mucigenous nature. This is a general characteristic of all the diverse anatomical forms of primary cancer of the lung (hilar infiltrative, massive with one large nodule, or with multiple nodules) and as is known its histological nature may vary from case to case.

The epidermoid or squamous cell histological type was not represented in our cases. We certainly do not know to what degree this exclusion is valid, but even in other case histories (Botteri, Liberti and Stella) which include the pleural form, no reference is made to this latter oncotype.

From an histological viewpoint another aspect should be emphasized. On the surface of the pleura the neoplastic tissue is always associated with a stromatic collagenous component which is particularly abundant, and which attains even greater prevalence than the quota of epithelial cells. This basic hyperplastic reaction, is in part induced by the infiltration of neoplastic elements, and is partially accentuated by phenomena of stasis in the subpleural lymphatic network (Scalfi[10]). The above reaction sometimes causes a considerable alteration in the arrangement of the infiltrated cellular nests, which brings about a complete lack of con-

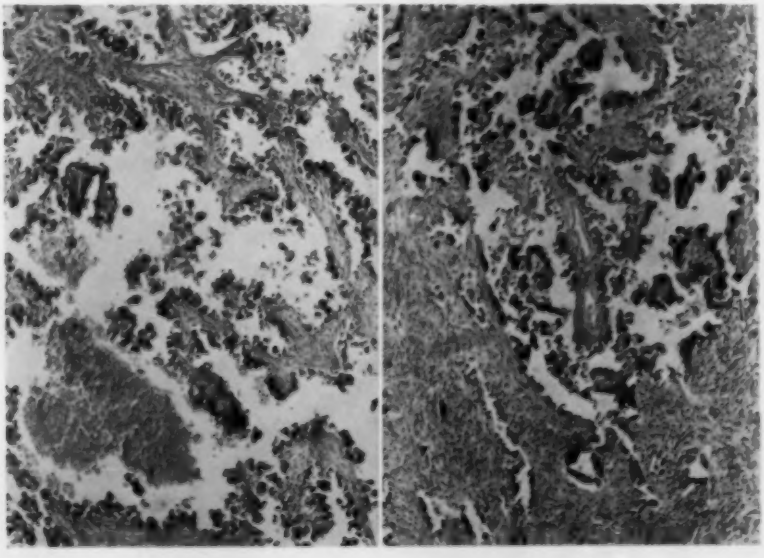

FIGURE 6A FIGURE 6B

Figure 6A (Case IV): Parenchymal fragment: neoplastic tissue constituted by cylindrical-cuboid epithelium, in a papillary arrangement.—*Figure 6B* (Case 4): Pleural fragment: same aspect, with a larger participation of connective stroma.

nection between the nature of heteroplastic tissues in the lung and those in the area of the pleura.

In this way, while in the lung there are varying types of arrangement, such as islands and solid cords, or tubercular, trabecular, papillar, adenomatous, etc., in the pleural area there is more commonly found a scirrhous type, with cellular formations of varying density, in which solid formations in general predominate. Of much greater rarity and of a barely perceptible type are trabecular and papillar formations, and those which resemble glandular formations (See figures 6 and 7).

Although the factors considered up to the present attribute to the pleural form of primary cancer of the lung certain characteristics which define with considerable clarity its clinical and anatomical physiognomy, they do not explain the causes and conditions which bring about the configuration of this complex structure. The fact that it is not brought about by single histological substrate, but that nearly all the cellular types of broncho-alveolar carcinoma contribute to its structure makes it still more difficult to determine the effective morphogenetic phases involved.

From the pattern of our cases and the examination of the observations of researchers who have preceded us, it seems possible to outline two conditions which are capable of giving rise to a surface development of primary tumor of the lung: Origin in subpleural and absolutely peripheral parenchymal sectors, and initial location in broncho-alveolar sectors immediately adjacent to the mediastinal pleura.

The attached diagram indicates this double possibility which in all

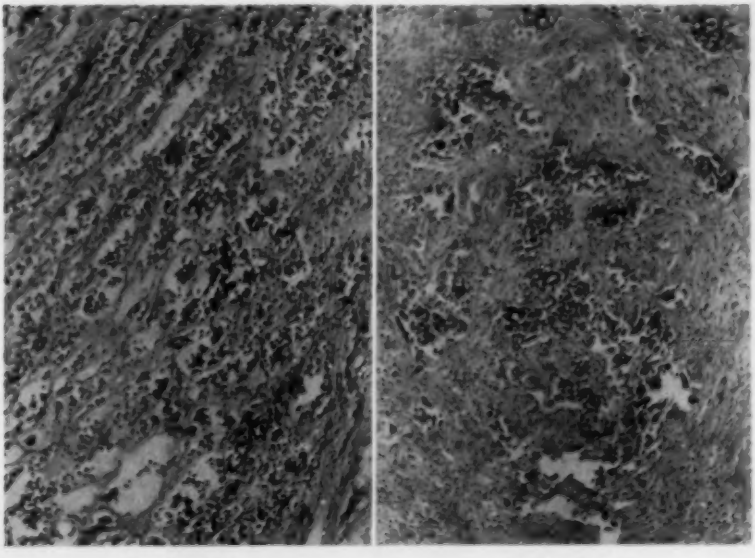

FIGURE 7A FIGURE 7B

Figure 7A (CASE V): Parenchymal fragment: neoplastic tissue of the kind of small-cell cancer.—*Figure 7B* (CASE V): Pleural fragment: nests of neoplastic cells on the background of a thick collagen tissue.

probability is to be considered linked to the adjacency of heteroplastic tissue of neoplasm to the pleural lymphatic network; this also leads one to believe that even in the first hypothesis the conditions which favor surface development may be given by propagation in a direct sense of the lymphatic stream; in the second hypothesis one finds a retrograde tendency, which also appears to lead to an extensive affection of the pleural covering.

Far from being explanatory, this statement is only a determination of the circumstances which bring about the anatomical picture in question. As in each individual sector of general and specialized oncology, there are numerous obscure points which the information and knowledge in our possession at present are insufficient to clarify.

SUMMARY

The pleural form of the primary cancer of the lung constitutes an infrequent, but absolutely particular type among the neoplastic lung processes. Its chief characteristic is that the neoplastic tissue, instead of involving the depth of the parenchyma of the lung, is almost entirely spread upon the pleural surface, becoming very similar to primary cancer of the pleura.

The histological analysis allows to differentiate it by finding cellular elements of broncho-alveolar derivations.

The authors have collected five cases of the pleural form out of a total group of 82 cases of primary cancer of the lung: in one of these a biopsy through pleuroscopy established the right diagnosis.

RESUMEN

La forma pleura del cáncer primitivo del pulmón constituye un tipo poco frecuente, pero muy peculiar entre los procesos neoplásicos pulmonares.

FIGURE 8: Scheme of possible morphogenetic derivations of the pleural form of primary lung cancer.

Su característica principal es que en lugar de invadir la profundidad del parénquima pulmonar se extiende casi completamente sobre la superficie pleural haciéndose muy semejante al cáncer primario de la pleura.

El análisis histológico permite diferenciarlo al encontrar los elemontos celulares de las derivaciones broncoalveolares.

Los autores han reunido cinco casos de la forma pleural de un total de 82 casos de cáncer pulmonar; en uno de estos una biopsia a través de la pleuroscopía estableció el diagnóstico correcto.

RESUME

La forme pleurale du cancer primitif du poumon constitue un type peu habituel mais tout à fait particulier des néoplasies pulmonaires. Sa caractéristique majeurs est que le tissu néoplasique au lieu de se développer dans la profondeur du parenchyme du poumon s'étend presque en totalité sur la surface pleurale, devenant très semblable à un cancer primitif de la plèvre.

L'analyse histologique permet de la différencier par la constatation d'éléments cellulaires d'origine broncho-alvéolaire.

Les auteurs ont recueilli cinq cas de forme pleurale sur un groupe total de 82 cas de cancers primitifs du poumon: dans l'un d'eux une pleuroscopie avec biopsie permit d'établir le diagnostic correct.

ZUSAMMENFASSUNG

Die pleurale Form des primären Lungenkarzinoms stellt einen seltenen, aber durchaus besonderen Typ unter den Lungenneoplasmen dar. Das Hauptkennzeichen dieser Art von Karzinom ist die fast ausschliessliche Ausbreitung neoplastischen Gewebes auf die pleurale Oberfläche an Stelle des Vordringens in die Tiefe des Lungenparenchyms. Somit wird dieser Krebs dem primären Pleurakarzinom sehr ähnlich.

Die Differenzierung ist durch die histologische Untersuchung möglich, indem zelluläre Elemente broncho-alveolären Ursprungs bei dieser Tumor-Art nachgewiesen werden können.

Die Verfasser haben 5 Fälle der pleuralen Form unter insgesamt 82 Fällen von primärem Lungenkarzinom gesammelt; in einem Fall wurde die richtige Diagnose durch thorakoskopische Probe-Excision gestellt.

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Bacteriologic Diagnosis of Tuberculosis in Mentally Ill Patients*

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It is hard to handle and to treat a mentally ill tuberculosis patient. His tuberculosis governs the field of treatment often to the detriment of his mental condition.

The impossibility to impose the rules of elementary hygiene on the mentally ill is chiefly responsible for the high incidence of tuberculosis among the patients of mental institutions. In 1950, the 231 institutions for mentally ill in the United States, with the total population of 511,064, reported 13,911 cases of active tuberculosis, that is 2700 per 100,000 inmates, compared with the 80 cases in the general population of this country. (Bettag, 1952.)

To prevent the spread of this disease, the early diagnosis of open tuberculosis is of utmost importance in mental institutions. Obtaining the necessary material for the diagnosis from a mentally ill patient is connected with great difficulties. Due to their aggressive behavior there are patients at Anoka State Hospital from which such material can be obtained only rarely. It is almost impossible to collect the most important material for tuberculosis diagnosis, sputum, from a mentally ill person. According to Burns, 1945, in the institutions for the mentally ill of Minnesota it was extremely difficult to get a specimen of sputum from more than 2 or 3 per cent of the patients. Even though cooperative, the mentally ill patient rarely understands the difference between sputum and saliva. Consequently, the most suitable material available, would be a gastric specimen. Unfortunately, gastric lavage is a long and disagreeable procedure among mentally ill people. This is particularly true if the first lavage is not easily performed. These circumstances motivated our attempts to find an easier way to collect pathologic material for tuberculosis diagnosis.

The laryngeal swab for collecting tuberculosis material is recognized as an easier, more rapid and less time consuming procedure for collecting tuberculosis material than gastric lavage. We investigated the usefulness of this method in mentally ill patients.

Material

From the 422 tuberculous mentally ill at Anoka State Hospital we selected 100 male and 100 female patients who, according to their most recent lavages, were positive for tubercle bacilli. These patients were positive by gastric lavage:

*From the Tuberculosis Research Laboratory, Anoka State Hospital, Minnesota. J. H. Reitmann, M.D., Superintendent; G. Fahr, M.D., Medical Director.

Years ago	0	1	2	3	4	over 4
Patients examined	114	52	13	5	10	6
Per cent	57	26	6.5	2.5	5	3
Standard error	±3.5	±3.1	±1.7	±1.1	±1.5	±1.2

Thus, among 200 investigated, 114 or 57 ± 3.5 per cent had shown positive gastric lavage results for tubercle bacilli in the last year. The rest of them, that is all but six, had been found positive in the course of the last four years. The total number of their gastric lavages examined before we started our work with these 200 patients was 2,681, or an average of 13.4 per patient. In 1,151 instances, or 42.9 ± 0.95 per cent, the gastric lavages had been positive, in 1,530 or 57.1 ± 0.95 per cent had been negative for tubercle bacilli. All 200 were subjected to one gastric lavage, and one laryngeal swab was taken from each patient.

Method

The cultivation of gastric specimens, collected in sterile bottles containing sodium phosphate as preservative, was carried out at the State Health Laboratory in Minneapolis, where the material from Anoka was delivered on the day of collection. The cultivation of swab material was performed in the laboratory at Anoka State Hospital.

Our swab consists of a piece of wire eight inches long, slightly bent, corresponding to the curve of the tongue and carrying a ball of gauze. The swab was sterilized in autoclave in a centrifuge tube. The operator passes the swab into the larynx until coughing is provoked.

The quantity of tuberculous material obtained by the swab is small in comparison to the amount obtained by gastric washing. In some cases the material on the swab may contain only a small number of bacilli. Because of this, the concentrating method of bacilli, described by one of us (Darzins, 1951) was applied to the swab material. This technique has been recognized as far superior to sulfuric acid procedure for culturing of a small number of bacilli (Weidmann, 1952; Mitscherlich, Reuss, Gürtürk, 1952).

The swab extracted from the larynx was returned to the centrifuge tube and covered with 10 ml. of purifier (mixture of 1 per cent NaOH and 1 per cent Na_3PO_4 .12 H_2O), thoroughly washed and drained on the walls of the tube; the second washing of the swabs was done in 2 ml. of saline, and both liquids were united. After resting for 1 hour at room t°, with occasional shaking of the tubes, 1 ml. of 1 per cent sterile solution of calcium chloride was added to the tubes and mixed with the purifier. Abundant flocculation of gelatinous calcium phosphate appeared:

$$2\ Na_3PO_4 + 3CaCl_2 = Ca_3\ (PO_4)_2 + 6\ NaCl$$

After the tubes had been centrifuged for five minutes, the clear supernatant liquid was discarded. To the precipitate on the bottom, 0.3 ml. of solvent (mixture of citric acid 3 g., ammonium citrate 2.5 g., sodium citrate 2 g., distilled water 100 ml., sterilized in an autoclave) was added.

The citrates dissolve unsoluble calcium phosphate and neutralize the alkalies so that the concentrated material can be inoculated by means of an ordinary pipette in the media. Two tubes of solid egg-potato medium and one tube of our liquid medium (described earlier) were used for each concentrated swab material. The solid medium was incubated at 37°C. for six weeks, the liquid medium was incubated for two weeks; thereupon the supernatant clear liquid was taken off the deposit with a pipette, approximately 0.5 ml. of the deposit was spread over the slide, dried and stained with Ziehl-Neelsen carbolfuchsin, decolorized with acid alcohol and counterstained with half saturated picric acid dissolved in water.

Results

The gastric lavages, as reported by the State Health Laboratory, gave positive results for tubercle bacilli in 61 patients, or 30.5 ± 3.3 per cent of the investigated. Swabs from the same patients revealed 49 or 24.5 ± 3.0 per cent positive results. Both gastric lavage and swabs revealed 76, or 38 ± 3.3 per cent positive cases. The liquid medium was positive in 33, that is 16.5 ± 2.6 per cent cases; in 3 instances only did the liquid medium reveal tubercle bacilli.

Efficiency of gastric lavage and swab methods in detecting tubercle bacilli in 200 mentally ill patients:

Procedure and Medium	Positive For Tubercle Bacilli	Per Cent Positive Standard Error
Gastric lavage, solid medium	61	30.5 ± 3.3
Swabs, solid and liquid media	49	24.5 ± 3.0
Gastric lavage and swabs	76	38.0 ± 3.4
Swabs, solid medium	46	23.0 ± 2.3
Swabs, liquid medium	33	16.5 ± 2.6
Swabs, positive in liquid medium only	3	1.5 ± 0.9

Addition of one laryngeal swab to one gastric lavage increased the total positive result by 7.5 per cent. Gastric lavage was positive in 45 per cent male and 31 per cent female patients. The "esthetic factor," greater swallowing of sputum on the part of female than male patients (Robinson and Dunn, 1943) was lost in mentally ill patients.

The liquid medium gave early positive results and information concerning the pathogenic properties of the bacilli. The colonies grown in the liquid medium could be detected by a microscope lens of low power and showed the characteristic growth pattern of pathogenic mammalian tubercle bacilli, namely the cord formation.

Out of inoculated tubes, eight with solid medium and four with liquid medium were lost because of contamination.

Discussion

The gastric specimens produced 6 per cent more positive cultures than concentrated material from swabs. It is questionable whether this differ-

ence arises from the greater efficiency of the gastric method as compared to the swab procedure. Statistically, this difference is not significant.

SUMMARY

The causes for the high incidence of tuberculosis in mentally ill patients were indicated. The absence of sputum and the difficulty of obtaining gastric specimens from such patients makes the diagnosis of tuberculosis difficult. The efficiency of the concentrated laryngeal swab technique for cultivation of a small number of tubercle bacilli was compared with the efficiency of gastric lavage in 200 mentally ill tuberculous patients. Solid and liquid media were used for the cultivation of laryngeal swab material. One gastric lavage produced 30.5 per cent, one laryngeal swab gave 24.5 per cent positive cultures of tubercle bacilli. One laryngeal swab added 7.5 per cent positive cases to those detected by gastric lavage. The liquid medium produced 16.5 per cent early cultures and revealed the pathogenicity factor, the cord formation, of the bacilli. The "esthetic factor," greater swallowing of sputum in females than in males, is lost in mentally ill patients.

RESUMEN

Se indicaron las causas de la elevada frecuencia de la tuberculosis entre los enfermos mentales.

La ausencia de esputos y la dificult ad para obtener lavados gástricos hace el diagnóstico de tuberculosis, más difícil. Se comparó la eficiencia del método de los frotis de laringe por cultivo de pequeño número de gérmenes con el lavado gástrico, en 200 enfermos mentales. Para los cultivos de los productos laríngeos se usaron medios sœlidos y líquidos. Con un lavado gástrico se obtuvieron 30.5 por ciento. Con un frotis laríngeo se obtuvieron 24.5 por ciento de cultivos positivos.

Un frotis laríngeo agregó 8.5 por ciento a los obtenidos por lavabo gástrico. El medio líquido dió 16.5 de cultivos positivos y reveló el factor de patogenicidad del bacilo, la formación de cuer das del mismo.

El "factor estético," consistente en que es mayor el número de mujeres que degluten sus esputos que los hombres, no existe entre los enfermos mentales.

RESUME

Les auteurs indiquent les causes du taux élevé de tuberculeux parmi les malades mentaux. L'absence d'expectoration et la difficulté d'obtenir des examens gastriques chez de tels malades rend le diagnostic difficile. La valeur de la culture par la technique de l'écouvillonnage laryngé est comparée à la valeur du tubage gastrique chez 200 malades mentaux tuberculeux paucibacillaires. Des milieux solides et liquides furent utilisés pour la culture par écouvillonnage laryngé. Par tubage gastrique, on obtint 30,5% de cultures positives, l'écouvillonnage en donna 24,5%. Le milieu liquide donna 16,5% de cultures rapides et permit de mettre en évidence l'élément déterminant du caractère pathogène du bacille: sa disposition en torsades.

Le facteur "esthétique," incitant les femmes à cracher moins que les hommes, ne se retrouve pas chez les malades mentaux.

ZUSAMMENFASSUNG

Die Ursachen für das häufige Vorkommen von Tuberkulose bei geisteskranken Patienten werden angezeigt. Das Fehlen von Sputum und die Schwierigkeit, Magensaftpräparate von solchen Kranken zu erhalten, macht die Diagnose einer Tuberkulose schwierig. Die Wirksamkeit der konzentrierten Kehlkopfabstrich-Technik zur Züchtung einer kleinen Menge von Tuberkelbazillen wurde verglichen mit der Wirksamkeit von Magenspülungen bei 200 geisteskranken tuberkulösen Patienten. Feste und flüssige Nährböden fanden Verwendung für die Kulturen des Kehlkopf-Abstrich-Materials. Ein Magensaft ergab 30,5% ein Kehlkopfabstrich gab 24,5% positive Kulturen von Tuberkelbazillen. Ein Kehlkopfabstrich fügte 8,5% positive Fälle zu den durch Magensaft entdeckten hinzu. Der flüssige Nährboden führte zu 16,5% frühen Kulturen und deckte den pathogenetischen Faktor des Bazillus auf, nämlich die Strangbildung. Der "aesthetische Faktor," wonach Frauen mehr Sputum verschlucken als Männer, geht bei geisteskranken Patienten verloren.

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Spontaneous Pneumohemothorax

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The syndrome of spontaneous pneumohemothorax consists in the idiopathic appearance of air and blood successively in the pleural cavity in association with varying degrees of pulmonary collapse. Laennec described the condition, wrongly attributing the air to the decomposition of blood. Whittaker is reported to have treated a typical case successfully in 1876. However, the first identified case reports appeared in the literature in 1900,[1, 2] with subsequent additions at decreasing intervals. Perusal of the details of the reported cases reveals frequently the presence of trauma, infection, or tumor in an etiologic position. This report is concerned with a study of the truly idopathic cases (116) among the many reviewed from the literature.[1-70] All others have been omitted. In addition, there are included four cases hitherto unreported. This does not purport to be a complete study of all the literature, although consciously only those cases of the Anglo-American literature have been omitted for which a cause can be found or of which sufficient details were not reported. This latter group was mainly comprised of cases which were included in studies of unrelated pathologic conditions.

Case 1: While painting a ceiling, this 24 year old white salesman suddenly developed severe, sharp substernal pain radiating to the right shoulder. This was associated with marked dyspnea and mild weakness. The family physician made a telephonic diagnosis of muscle strain, advising rest and analgesics. During the succeeding 72 hours the symptoms receded. However, because of their persistence and because of the appearance of a mild nonproductive cough, the patient, after an additional three days, reported to his physician, who diagnosed hydropneumothorax and referred him for admission to the U. S. Public Health Service Hospital, Seattle, Washington, on the same day, the seventh of his illness. The past history and systems review were negative. Physical examination revealed a visible and palpable lag of the right hemithorax, with decreased tactile fremitus and absent breath sounds. A succussion splash was noted. There was no mediastinal shift or objective distress. X-ray film revealed virtually complete collapse of the right lung with fluid level at the 11th rib posteriorly. Second strength purified protein derivatives caused no reaction. The hemogram was within normal limits. An immediate diagnostic thoracentesis resulted in removal of 20 cc. of bloody fluid. During the next 10 days, four subsequent thoracenteses yielded 1,360 cc. of bloody fluid. The temperature was slightly elevated to 100° F. or less during the first 10 days of hospitalization. Fluoroscopy and x-ray film revealed progressive pulmonary reexpansion which became complete after five weeks.

Case 2: While boarding a bus, this 27 year old white male airplane parts cleaner developed sharp, left mid chest pain, which radiated down the left arm and was accompanied by dyspnea. Two days later, because of persistence of symptoms, he reported to his physician who diagnosed collapsed lung and, after hospitalization, removed air and 700 cc. of bloody fluid, with marked relief of symptoms. After transfusion and because of resurgence of symptoms, the patient was transferred to the U. S. Public Health Service Hospital, Seattle, on the ninth day of illness. Past history and systems review were negative. Physical examination revealed the physical findings of left hydropneumothorax with moderate mediastinal shift. The hemogram was normal. X-ray film revealed marked collapse of the left lung, with a fluid level at the lower border of the anterior margin of the third rib. Thoracentesis on the day of admission yielded 1,400 cc. of bloody fluid with hemoglobin content of 7.3 Gm. per cent. On the following day 1,200 cc. of air were removed, with almost complete reexpansion

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All four patients were hospitalized as beneficiaries of the Veterans Administration.

noted on x-ray film that same day. The remainder of hospitalization was brief and uneventful. He was discharged three weeks after the onset of illness. During the first three days of hospitalization, he exhibited temperature elevations of less than one degree on two occasions.

Case 3: A 29 year old white male grocery clerk noted gradual onset of vague anterior chest discomfort and mild dyspnea, both of which he attributed to severe hay fever. During the next 24 hours the symptoms became more severe, prompting a visit to a physician, who made a diagnosis of muscle strain. In spite of symptomatic treatment, the pain and dyspnea became more severe, ultimately resulting in hospitalization and the diagnosis of hydropneumothorax. Institutionalization lasted nine days and consisted of bed rest and antibiotics. The course was uneventful, afebrile, and marked by progressive resorption of the intrapleural fluid. Ten days after discharge he developed fever, mild respiratory distress, and moderately severe dull pain in the left chest, shoulder, and left upper abdomen. Rehospitalization revealed an increase in pleural fluid. A diagnostic tap, the first thoracentesis, resulted in the removal of 50 cc. of bloody fluid. He was returned to his home where he experienced an exacerbation of symptoms, which resulted in admission to the U. S. Public Health Service Hospital, Seattle. The past history and systems review were noncontributory, excepting four episodes of dyspnea, left chest pain, diaphoresis, and vomiting, which were experienced in the five years preceding the onset of the present illness. He denied intercurrent symptoms and stated that two chest x-ray films during these years were interpreted as normal. On admission, moderate dyspnea and temperature of 100.2° F. were noted. The trachea was displaced to the right, and left hemithoracic lag with dullness and absent breath sounds was noted. There was guarding and tenderness of the left upper abdomen. The hemoglobin was 11.5 Gm., the red blood count 3,470,000, and the hematocrit 35. Chest roentgenograms revealed mediastinal shift to the right, with complete obscuring of the left lung field by a density greater than that of the cardiac shadow. Serial films after thoracentesis revealed almost complete collapse of the left lung. Thoracentesis on the day following admission produced 250 cc. of bloody fluid. On 12 subsequent occasions during the next four weeks the procedure was repeated, with a total 4,229 cc. of fluid obtained of which more than 4,200 cc. were bloody and were obtained during the first 14 days of hospitalization. Incident to these procedures approximately 1,500 cc. of air were introduced intrapleurally. During the first 26 days he exhibited low grade temperature which only once reached 101° F. He received 2,000 cc. of whole blood and prophylactic antibiotics during hospitalization. Pulmonary reexpansion was progressive but slow due to loculation of fluid and air. According to several observers, the introduction of air seemed to impede reexpansion. After two months of hospitalization, there was almost complete reexpansion and only minimal amounts of residual fluid. Accordingly, he was discharged and permitted to return to work after two additional weeks of convalescence.

Case 4: One week after the onset of mild upper respiratory infection this 32 year old white male office worker, while seated, experienced a moderate bout of coughing followed by sharp pleuritic right chest pain over the same area involved by mild pleurisy in 1937. Increase in the severity of pain and the appearance of minimal dyspnea precipitated admission to another institution where a small apical pneumothorax was noted. During the following 72 hours progressive fall from normal of the red blood count to slightly more than 3,000,000 and of the hemoglobin to 8 Gm. was associated with persistent weakness. Repeat chest roentgenogram revealed mediastinal shift to the left and fluid level at the second rib which obscured the entire right chest. Thoracentesis on the third day yielded 1,000 cc. of bloody fluid and included air replacement. This was repeated on three subsequent occasions, with removal of almost all fluid and marked reexpansion although an irregular radiopaque density in the right base persisted. Three thousand cc. of whole blood were given and he transferred to the U. S. Public Health Service Hospital, Seattle, on the 22nd day of illness. The past history and systems review were otherwise noncontributory. Examination revealed an ill-appearing, perspiring male whose only abnormal physical findings were those of hydropneumothorax without mediastinal displacement. Chest roentgenogram revealed moderate pulmonary collapse with basal fluid and air pockets. On the following day, under endotracheal anesthesia decortication was performed. Careful search of lung surface and parietal pleura failed to reveal any abnormality from which the original hemorrhage might have occurred. The right thorax contained a large encapsulated mass of old dark blood. Adhesions were noted between the superior and middle and between the superior and inferior lobes, in the minor and major fissures, respectively. The anterior superior portion of the upper lobe and the anterior portion of the middle lobe, as well as the mediastinal surfaces of these lobes, were not covered by the fibrous capsule. The inferior lobe was collapsed against the mediastinum and its inferior portion adherent to the diaphragm. Five fibrous adhesions between the lung and the anterior chest wall were noted. Approximately one liter of old blood was

removed. Microscopic examination of the membrane revealed a sheet of cellular granulation tissue infiltrated by a small to moderate number of inflammatory cells including lymphocytes, plasmacytes, large mononuclear cells, and fewer neutrophils. No microorganisms were noted, nor was there evidence to suggest specific etiology. Focally phagocytosed hemosiderin was noted. On the surface there was clotted blood showing beginning organization. Postoperatively he had some difficulty with right pneumothorax but convalesced smoothly and showed progressive pulmonary reexpansion until chest roentgenogram showed the lung was but 2 cm. from the chest wall. He was discharged from the hospital on the 23rd postoperative day. On the fifth day after discharge the developed left chest pain of a pleuritic type, which persisted and precipitated readmission after 24 hours. Examination revealed findings consistent with left pneumothorax and thickening of the right basal pleura. The former was confirmed on x-ray film. Symptoms disappeared without specific therapy, and he was discharged after one week's hospitalization. Follow-up chest roentgenograms two weeks later revealed complete reexpansion of the left lung with no further change in the right base.

Pathogenesis

There are many proposed causes for spontaneous pneumohemothorax, none of which is universally accepted. Principally these include congenital or acquired defects of the pleura, silent nondemonstrable tuberculosis, rupture of vascular adhesions due to abrupt shift from shallow to deep respiration, rupture of a single emphysematous bleb or of a valve vesicle arising from healed apical scars or local emphysematous changes without scar tissue.[74] Rupture of the elastic fibers in the subpleural alveoli into the areolar layer of the visceral pleura separates and elevates the latter, with, it has been suggested, tearing as air is forced from the bases of the lungs into the apices incident to activity.[73] This is assisted by the abdominal and expiratory musculature acting in combination with the closed glottis as a check valve.

Most significant is the work of Macklin,[76] involving experimental insufflation of cats' lungs to produce pneumothorax. He demonstrated that air escapes from the alveoli along the perivascular sheaths and through the interstitial tissues to the mediastinum. After a sufficient amount of air has collected there, the thin mediastinal wall ruptures into the pleural cavity. Macklin could not demonstrate rupture of the pleural surface. He hypothesized that in man a peripheral endobronchial ball valve, in the form of a mucus plug, permitted the entrance but not the escape of air and so provided a similar mechanism. Of course, the air may travel peripherally along perivascular sheaths to cause subpleural blebs. These are subject to rupture incident to pressure changes. While these latter mechanisms may well be common, undoubtedly alternate mechanisms occur. The existence of these perivascular spaces has been demonstrated by other observers.[71]

Pathology

Much of the early literature is concerned with speculation over the customary coagulation failure of blood withdrawn by thoracentesis. Currently it is generally conceded that this defect is due to early defibrination incident to the whipping action of the heart and lungs. The clotting of blood after withdrawal is consistent with extremely recent or continuing hemorrhage. Pleural exudation contains increasing amounts of fibrinogen and may cause coagulation when thoracentesis is performed late in the

course of the disease. Previously, consideration was given to blood replacement in the form of the material withdrawn from the chest. Such a procedure is inadvisable and unnecessary at this time. The hemorrhagic fluid obtained via thoracentesis contains little fibrinogen and has a hemoglobin content approximating 30 to 50 per cent of that found in the circulating blood. Initially, of course, it is virtually identical with the systemic blood. Later it contains increasingly large amounts of fibrinogen.[72, 75] This latter is a major reason for early therapy.

It seems apparent that the only difference between spontaneous pneumothorax and spontaneous pneumohemothorax is intrathoracic hemorrhage. This differentiating feature arises from torn pleural adhesions or the occurrence of a tear through an unusually well-vascularized segment of pleura. Pleural adhesions of varying degrees have been noted to be present in most adults, frequently without history of infection. While a few of the reviewed case reports mentioned details of previous pulmonary infections to which one could ascribe adhesions, more than 90 per cent contained no such information.

The parietal pleural blood vessels present a systemic pressure approximating six times that of the pulmonary vessels, which latter tend to compression with the collapse of lung tissue. Moreover, the intrathoracic blood and air exert a more hemostatic effect on the lesser pressured circulation. One would expect the more severe hemorrhage to arise from the parietal remnants of pleural adhesions rather than from ruptured bullae or visceral remnants of adhesions. Of course, associated adhesions which prevent effective pulmonary collapse may promulgate bleeding. Rarely bullae exhibit marked vascularization.

Sixteen deaths due to spontaneous pneumohemothorax have been reported, along with the autopsy findings.[1-16] Although mortality is approximately 14 per cent, most of these deaths occurred before the availability of whole blood transfusions and ready, safe thoracic surgery. Thus it is apparent that the condition is more benign than the above figure indicates.

Review of postmortem findings reveals failure to discover definitely the cause or the source of bleeding in the majority of cases. Reports of postmortem in 16 deaths noted the presence of apical scars in 11, viscero-parieto-pleural adhesions in 10, and bullae in 12 cases. In one recovered case, subsequently autopsied after death due to malignancy, blebs were noted. In seven of the fatal cases the authors discovered no apparent cause for the rupture or site of hemorrhage. Five of the episodes were attributed to tearing of adhesions, two to ruptured bullae, and three to a combination of the two factors. In three the authors specifically reported that no causative lesion could be discovered. Commonly the site of bleeding was inferred rather than demonstrated. Of 28 cases treated surgically the authors stated specifically that they could find no cause for collapse in four or for bleeding in two. Adhesions were noted in seven and blebs in nine. Adhesions were the site of bleeding in five and a branch of the subclavian vein in one. In four the collapse was blamed on lung lacerations (nonspecified) and in two on ruptured bleb. It is apparent that the vast

majority of authors did not make any mention of surgically demonstrable lesions. Of course, 23 of the procedures consisted of decortication after the lung had been encased in a fibrous membrane which obscured the initial lesions.

Clinical Syndrome

Characteristically, the patient abruptly develops severe, continuous chest pain, which is usually described as sharp. Frequently there is radiation to the shoulder, back, or upper abdomen. Invariably there is a feeling of weakness, occasionally terminating in syncope or shock. This latter usually occurs some time after the onset of pain and is related to the degree of intrathoracic hemorrhage although the pain may be of sufficient severity to precipitate shock. Dsypnea is common but, by and large, not severe.

The foregoing are the salient features of spontaneous pneumohemothorax and appear constantly, as described, in virtually all of the reported cases. Rarely the symptoms are limited to, or point primarily to, the abdomen and precipitate abdominal surgery.

Sex incidence: Typically the patient is a young male. Among the 120 cases reviewed only eight occurred in females. The reason for the predominance of males is not apparent.

Age: Spontaneous pneumohemothorax is a disease of the young adult. All but nine cases of the present series involved persons 39 and under. The youngest case was that of a 14 year old boy. Eleven cases occurred in those 19 or under, 64 in the 20 to 29 group, 35 in the 30 to 39 group, nine in the 40 to 49 group, and one in a 51 year old male.

Location: While not noted in three cases, the pathology was reported as left-sided in 66 and right-sided in 51 cases. Although this difference is not significant, it is difficult to explain the predominance of right-sided lesions among the fatal cases; i.e., 11 vs. five. The operational factors in this group may well be identical with those which come into play in the hypotension and cardiac dysfunction evident in the left lateral position.

Fever: Of the cases reviewed, 36 were noted to have exhibited a temperature elevation which was invariably low grade and of less than one week in duration. Since many case reports were summarized briefly, it is probable that a much larger percentage of cases had a mildly febrile course during the first week. Continued or high temperatures should prompt study for complications.

Physical findings: The physical findings are usually limited to the chest and are those of pneumothorax and hydrothorax. In almost every reported case there is notation of tracheal deviation. Evidences of shock and anemia may be present. Frequently there is some upper abdominal guarding and tenderness. On occasion this has been so marked and in association with sufficient muscle rigidity and rebound tenderness as to lead to exploratory laparotomy.

Laboratory findings: The chest roentgenogram shows evidence of varying degrees of pneumothorax and hydrothorax, although not concurrently initially. Occasionally pleural adhesions or bullae can be discerned. Serial

hemograms reveal developing anemia. Other laboratory tests are of little value except in the negative sense of ruling out other conditions or complications. Customarily hemorrhagic pleural fluid does not clot when withdrawn.

Treatment

In the past there was much controversy over the value of therapeutic thoracentesis and its temporal position in the treatment program. There is no longer anyone who objects to the complete removal of blood and air except in mild cases.[65] However, disagreement persists as to the rapidity with which this procedure should be initiated. Some authors have advocated waiting several days until there is clinical evidence that bleeding has ceased. This certainly is not justified on the basis of preventing anemia since the intrapleural blood is of no value to the patient. The delay of a few days while the intrapleural blood acts as a tamponade is justifiable provided the patient is constantly watched and surgical intervention sought as soon as the course becomes unsatisfactory. With the availability of whole blood and the safety of thoracic surgery, there is no longer an excuse for delayed intervention when conservative therapy fails. The latter chiefly consists of transfusions, oxygen, general supportive therapy, and repeated thoracentesis, particularly to correct mediastinal shift. In the face of continued hemorrhage or cardiorespiratory embarrassment arising from persistent mediastinal displacement, early thoracotomy is indicated. It would appear that regardless of the satisfactoriness of the clinical course, intrapleural blood and air should be aspirated as completely as possible. It is a simple and a safe procedure, well worth the effort. There seems to be no virtue in the replacement of blood by air. This procedure results in further pleural irritation and the maintenance of perfect potential culture area as well as tending to promulgate incomplete reexpansion. Unfortunately, early thoracentesis does not insure good results in every case since, of the 28 surgically treated, virtually all had early conservative therapy which failed. Nevertheless, examination of the case reports of this series reveals unequivocally that the speed and completeness of recovery are direct functions of early thoracentesis. There is no report of a second spontaneous pneumohemothorax in the same patient although such might have occurred in Goldman's patient,[42] who, approximately one year after the spontaneous pneumohemothorax, had a spontaneous pneumothorax with slight effusion but was not tapped.

Enzyme therapy in the form of streptokinase and streptodornase has been used successfully although it has been reported that application during the early stages may increase bleeding, presumably by fibrinolysis. Decortication may be necessary and is, with rare exception, associated with good results. However, with early thoracotomy and local excision and repair, this procedure will become less common in the cases which do not speedily respond to conservative therapy. Decortication achieved excellent results in 17 cases and good or fair results in three, with no evaluation of the procedure recorded in three although the implied results were good or fair. All of the early thoracotomies had excellent outcomes.

These figures speak well of early and late surgery, particularly of the former.

SUMMARY

One hundred and twenty cases of spontaneous pneumohemothorax have been reviewed and the pertinent data presented. Prompt and adequate treatment of this uncommon condition is essential if morbidity and mortality are to be reduced.

RESUMEN

Se han presentado una revisión de 120 casos de hemoneumotórax espontáneo así como los datos pertinentes. La atención pronta ya adecuada es necesaria para reducir la morbilidad y la mortalidad de esta afección poco común.

RESUME

L'auteur passe en revue 120 observations d'hémopneumothorax spontaé et présente des données qui en découlent logiquement. Il est essentiel que soit mis en oeuvre le traitement rapide et judicieux de cette affection peu fréquente si l'on veut réduire la morbidité et la mortalité.

ZUSAMMENFASSUNG

120 Fälle von spontanem Pneumo-Haemothorax wurden durchgesehen und die diesbezüglichen Werte vorgelegt. Prompte und adequate Behandlung dieses ungewöhnlichen Krankheitszustandes ist wesentlich, sollen Morbidität und Mortalität gemindert werden.

Complete reference list will appear in reprints.

The Role of Counseling Psychology in a Tuberculosis Hospital

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Introduction

This article is intended as an architect's sketch, or a blueprint for a counseling program rather than a finished structure. Oversimplification of complex situations is readily admitted. If it serves to stimulate a little thought about a finished structure or about the material with which it might be built, then it will have served its purpose.

The Problem

No one will dispute the desirability of fitting the round peg in the round hole and the square peg in the square hole. But it is easy to forget that when the peg is a human individual and the hole is a niche in human society neither is perfectly round nor square. Nor are their shapes constant. Adaptations in both the individual and society are continually needed to make better "fits." The attempted adaptation frequently results in a poorer fit below the surface even though the fit at the surface appears to be good. The peg becomes wobbly, or bent, or so loose it falls out, or so tight it cracks. These attempted adaptations have often shaped the peg—the human individual—in a fashion that limits greatly the number of holes he can fit. Further adaptations—more realistic ones—are often necessary.

Vocational counseling, attempting to facilitate better adaptations, is replacing vocational advising with its emphasis on finding a ready-made hole that the peg can fit.

Nature has endowed man with a remarkable power of adaptability. it has been estimated that the average individual is physically and mentally equipped to fulfill the requirements of about 30 job families with approximately 30 variations of jobs in each family, making possible a total of 30 times 30, or 900 occupational possibilities.[4] The gifted individual is even more fortunate. The field of choice is somewhat narrowed for the man handicapped by tuberculosis but still offers him considerable choice.

The greatest constrictor of a man's field of occupational choice is not his physical and mental capacity, but his pattern of acquired attitudes and emotional needs. This limits the variety of activities that can yield him satisfaction. Being acquired, or learned, they can be re-learned, or "un-relearned," or re-oriented. For the tuberculous patient the re-orientation of some of his attitudes must often be a primary goal of vocational counseling.

There are at least two reasons for this. The first and more obvious is that the removal of some of the constricting effect of personal attitudes

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will open up more occupations from which the patient may choose, thus increasing his chance of selecting a vocation that is physically compatible with his condition and one that offers a reasonable degree of employment security.

The second, and perhaps more important reason, is that these attitudes and emotional needs influence the man's total behavior, both at work and after working hours. He cannot leave one set of attitudes at home and take another set to work with him. He can deny expression to some of his attitudes and needs at work, but they will seek expression after working hours. They seek expression in behavior. Therefore his attitudes must be those which will stimulate behavior consistent with his tuberculous condition. Then his attitudes can be expressed through occupational activities consistent with his physical condition, and these activities can then satisfy the emotional needs which are associated with his attitudes. In other words, he can gain satisfaction from an appropriate occupation.

Vocational counseling, then, must deal with attitudes. In fact all counseling whether it be aimed at vocational adjustment, marital adjustment, or adjustment in any other situation, deals with attitudes and attitudinal changes in people. Vocational adjustment is merely one aspect of a broader process of personal adjustment.[6]

Vocational counseling assists the individual to recognize some of the attitudes and biases he holds, and the influence of those attitudes on his vocational scheme of life. But his vocational life can no more be separated from his whole life pattern than the mind can be separated from the body. Each man's attitudes are all interrelated and integrated in his personality. Their unique configuration in each person is the basis of his individual personality. Thus in vocational counseling it becomes necessary to deal with attitudes toward family, toward authority, toward social institutions, and hundreds of things not directly associated with a specific occupation. And in tuberculous patients many of the attitudes developed as a result of the disease itself will influence occupational choice and vocational behavior.[2]

What are some of these attitudes? A few very common examples from the multitude of those existing in vocationally maladjusted people may clarify the preceding and following discussion.

1. "I'm too old to learn a new occupation." This is an extremely common attitude in people from all age groups, even those in their teens and twenties, not only elderly people. It is an attitude, and an unrealistic one. It is not a fact. The fact is that all people do learn and will learn every day they live, and their learning can be directed toward a new occupation if the necessity for it is accepted. The attitude mentioned was itself learned by the individual. It may have stemmed from lack of information or misinformation, or it may have grown out of a previously acquired attitude of not wanting to learn or preferring to live on a pension. If based on the latter preference, it can lead to a dependent state of mind, namely, that "since I cannot learn a new occupation and cannot return to my old one, it is society's duty to support me."

"Clerical work is not a man's job." Obviously this, too, is an attitude with an unrealistic basis. It cannot be a fact, since several million men earn a livelihood wholly or partially in clerical work. A common attitude, this one is particularly unfortunate in the mind of a tuberculous patient, since clerical work is generally compatible with the man's physical condition and is a comparatively common type of work. It is not restricted to any locality, industry, or level of difficulty. It generally requires only a short training period for minimal competence.

But an attitude like this example precludes choice of, or training in such an occupation. Even if the attitude is repressed to the subconscious to permit the work, it may retain its damaging qualities. The attitude, seeking expression as a liquid seeks its own level, may motivate behavior to emphasize the man's manliness: He may go mountain climbing, or keep late hours "drinking with the boys," or otherwise overtax himself to maintain his manhood in his own perception (and, he presumes, in the perception of his fellow men).

3. "I'm a strong man. I have stamina. I can outwalk, out-lift, and out-work any man in the crew." Before his tuberculosis, this attitude may have been realistic. It may have been a fact as well as an attitude. After having contracted tuberculosis it is no longer fact. And if the attitude still persists, even subconsciously, it probably indicates that the man's strength has served to compensate for some other felt inadequacy. The compensation may be even more needed if tuberculosis has served to increase the feeling of inadequacy. Further compensation, by denying the disabling effect of tuberculosis, may motivate feats of strength and stamina to demonstrate to himself (and presumably to the world) that he is as good a man as he ever was. Since the man feels good physically, this is easy to do and self-convincing is easy. But in a short time the result may be disastrous.

Conscious awareness of the attitude and the source of its development may either enable the person to change it, or may make it possible for a different compensation to replace the old one. Mental, educational, or economic feats might displace the feats of strength, for example.

The Aim of Counseling

What can be done about attitudes in tuberculosis patients? Probably nothing, if we don't discover what they are and from where they came. But we can discover a significant number of them and we can trace the development of some of them. And they are not permanent, rock-bound, immutable traits, for we continue to form and re-form them every day we live.

Some attitudes are much easier to influence than others. Those which are being formed from day to day in the hospital are in their infancy and their growth can be influenced a great deal *by the total hospital environment.*[1] Ordinarily they cannot be directed in their growth (their development is a growth process) to any appreciable extent by any one person, although sometimes one person influences another tremendously.

If the whole hospital environment is much more influential than any

individual, it follows that the whole staff—doctors, nurses, attendants, and all others—must influence the formation of a positive, optimistic approach to vocational problems. Without their help, the vocational counselor is seriously handicapped.

The newly forming attitudes must grow in the humus of thousands of older attitudes. These older, long-established, "matured" attitudes are much more difficult to modify. But as necessity is the mother of invention, so is it the mother of change; and the very necessity for change, when perceived in a realistic, undistorted way, can be a powerful tool in effecting at least some change. Enough has been done to demonstrate that the attempt is often not as futile as it appears to be beforehand.

What is the function of the counselor, then, in this total hospital environment?

As the patient begins to think about his problem, conflicting decisions come up. They are accompanied by emotions; the emotional conflict may be quite marked, since the life and well-being of the individual is at stake.

Conflicts arising may resemble these: "I can't go back to my former occupation, but for economic reasons I must resume it." "I need a light trade to protect my health, but that's impossible to start at my age." "I don't feel able to go back to work yet, but my family will think I'm slothful if I don't." "The doctor thinks it would be risky for me to leave the hospital this early, but I need to be home." "Hospital regimen is tough, but what's better about the world of work and worry?"

Such conflicts demand resolution in the patient's own mind one way or the other as soon as possible. Once resolved, related conflicts tend to be resolved in the same general direction.

The "peaks" of such conflicts may be considered "critical points" in personal adjustment, (and in vocational adjustment too if the conflict relates to earning a living). The maximum benefit of individual counseling might be obtained during these critical periods, by influencing the beginning direction which the resolution of conflicts will take.

The conflicts here regarded as "critical points" are not necessarily the highly emotionalized, obviously crippling states of mind that are usually associated with psychiatric treatment or abnormal psychology. Rather, they are the ordinary, everyday conflicts that are more often referred to as problems of decision. They are the ordinary conflicts which are generally resolved to the personal satisfaction of the individual without help, but are often resolved in socially unacceptable ways or in ways that lend immediate relief without regard for long-range planning. They are the ordinary conflicts whose maladaptive resolutions may lead to irregular discharges, dependency on public welfare, and other problems in society.

Obviously all patients do not require the same assistance in resolving their ordinary conflicts. Many come into the hospital with a history of good personal adjustment. They are people who have learned adequate habits of viewing themselves and their situation quite objectively, and have consequently resolved their problems in a realistic fashion. They

may need little or no psychological assistance, though they may need information. Others enter the hospital with a background of maladjustment. Their adjustment habits are faulty and inadequate, and need to be re-learned through guided practice in adjusting to each little problem situation that presents itself in the hospital environment.

A four-point counseling program might be proposed to facilitate the learning of adequate adjustment habits:

First, the counseling psychologist should take an active part in patient education and in the staff's in-service training. A counseling program is broader than the counselor; it requires cooperation of doctors, nurses, social workers, and other staff members who are daily influencing patients in their routine contacts. Through effective education the entire staff can become more effective in influencing patients, and patients may be induced to seek competent help in resolving their problems. Thus the patient identifies his own conflicts, which he probably can do better than anyone else since he alone experiences his own feelings. And each staff member can refer the patient to the person best qualified to help with any particular problem—the doctor, the vocational counselor, the social worker, or some other individual.

Second, conflicts may often be detected by routine contacts, aided by psychological testing, at times when such conflicts are highly probable. One such time is probably early in hospitalization, after the immediate emotional impact of the diagnosis has worn off. Another might be likely to occur when discharge from the hospital is imminent, when the patient goes to the ambulatory ward for the finale of hospital treatment. Perhaps there are others, and certainly there will be a great variance from patient to patient.

Third, counseling referrals may be made through ward rehabilitation conferences. The combined evaluations, discussion, and referral of several staff members should make more effective referrals, and at the same time contribute to the educational efforts mentioned in point one.

Fourth, the counseling psychologist should offer leadership in the application of effective counseling techniques by all professions represented in the hospital. Effective counseling has evolved from theory and techniques developed by several disciplines, notably psychiatry, psychology, social work and education.* These disciplines offer leadership, not monopoly. Only through utilization of available knowledge by all professions can society—and hospital treatment—make maximum progress.

Counseling As a Learning Situation

The basic tool of counseling is the interview. Tests are interview aids. It is through the interview that the patient can become aware of some of his biases, prejudices, and personal needs—some of his illogical attitudes and the source of their development.

*The reader who is interested in techniques for his own use and development would find a stimulating and thought-provoking "point of view" presentation in Rogers.[5] Thorne[7] has written an eclectic introduction to counseling methodology with a more traditional approach.

Awareness of his own attitudes may often suffice to enable the patient to recognize the illogical foundation on which the attitude was built. Counseling seeks to help the patient become aware of the attitudes which are unrealistically blocking the resolution of his conflicts. Perceiving the problem in a realistic way, including the attitudes involved, brings a realistic resolution of the conflict.

To illustrate, consider the sample conflicts mentioned above. The first, "I can't go back to my former occupation, but for economic reasons I must resume it," has a fact versus attitude element. "I can't go back to my former occupation" is a fact (assuming that preservation of health is vitally important) which has been well demonstrated by the sad experience of *many* others. But there is an "out" because it is also a fact that a *few* tuberculous patients have successfully resumed such work. That little "out" enables the attitude "I must resume the old occupation" to prevail over the fact of high probability of breakdown.

The patient perceived these alternatives as conflicting facts, not as fact versus attitude. The one "fact" was irrefutable while the other had a "maybe" attached. However big the "maybe" is, in his perception the conflict could be resolved in only one way.

Suppose he had perceived his need to return to the old job as a feeling based on immediate economic need and weighed it against the value of health. Or suppose he had considered long-range economic needs along with immediate needs. Perhaps a different occupation utilizing much of his skills and experience could have been suggested that would not entail a severe drop in wages.

Or he might have perceived (in some cases) his old occupation as a means of meeting a prestige need. This perception could have led to a search for another means of gaining prestige, or it could lead to an insight that the need which the job originally satisfied has long since vanished.

There are many other possibilities. But all of them are difficult for the patient to accept after his initial conflict has been resolved. He fights against re-opening the healed sore. But while the conflict is actively disturbing him, the patient is receptive to any suggestion that offers relief from the tension.

Counseling seeks to help the patient become aware of some of his feelings of need and the distorted perceptions based in part on those feelings. It is possible then for him to perceive his situation more realistically and base his actions a little less on emotion and a little more on reason.

But the most important outcome of counseling is not the resolution of each separate conflict. More important is the learning that occurs: The patient has learned to view himself and his feelings a little more objectively, and thus make a more adequate adjustment to a disquieting situation. Each new adjustment in which objective self-study is utilized serves to build habits of realistic adjustment. They are habits of apprais-

ing each situation more objectively, and will begin to operate in non-vocational problem situations as well as vocational.

Vocational counseling thus becomes a vehicle for training in all sorts of personal adjustments. Counseling in other areas (family problems, religious, or financial problems, etc.) could serve as a vehicle too. Probably the principal advantage of using vocational problems as a vehicle lies in their concreteness, ready acceptability by patients, and the fact that self-support through gainful employment is the capstone of the rehabilitation process.[3]

Conversely, adequate non-vocational adjustments result in the learning of habits which facilitate vocational adjustment. These are the habits that are commonly referred to as attitudes. Attitudes are mental habits—habitual thoughts—which are acquired according to the same laws of learning that operate in acquisition of arithmetic skills or reading skills.

Attitudes may be regarded as learned habitual thoughts. They are susceptible to change, or re-learning, according to the same principles of learning by which they were originally acquired. How? How does a child learn correct arithmetical habits? By practice over a long period of time—by drill—and most efficiently by *purposeful* practice such as he gets when he counts his own marbles, divides his own money, or adds his own scores while playing a game. In short he learns his arithmetic through experience in applying correct arithmetical habits to his own problems.

Likewise, through guided experience in problems of human adjustment and human relations he learns habits of personal adjustment. He learns habits of appraising himself and each problem situation in which he becomes involved with greater objectivity—habits of acting rationally rather than impulsively by successfully solving his problems through objective reasoning and recognition of his emotional attitudes or feelings.

Unfortunately, erratic habits can be learned too. Adults today don't often display erratic arithmetical habits because their early practice was guided with reasonable efficiency. But guidance in the development of social attitudes has often been lacking. Erratic habits of adjustment in adults are quite common. Can they be relearned or correctly learned at this late date? Who would suggest that any adult of normal intelligence cannot learn arithmetic if he has failed to learn it or has learned it incorrectly? Is it less reasonable to expect adults to learn new or correct thought habits relating to personal adjustment?

Of course the learner must first recognize and accept the incorrectness or inefficiency of his original set of habits, whether they be related to arithmetical problems or personal adjustment problems. The new learning must serve a purpose for him. It should offer him promise of helping himself out of fresh difficulties and problems as they arise.

When is the tuberculous patient likely to accept in his own mind the inadequacy of his own set of adjustment habits? Probably when they fail to help him solve a problem—when he is frustrated—when he has an emotional conflict. Many an experienced chronic patient can then offer him a solution but from a societal standpoint it may be another incorrect

or ineffective one. The blind will lead the blind if leadership with vision is unavailable.

Counseling can offer the patient relief from his conflicts by providing him realistic help when he needs it. The patient must learn that help is available or he cannot request it.

Counseling—not counselor—was suggested. Let that be re-emphasized. Counseling is not a monopoly of psychology, nursing, medicine, or any other profession. It is a skill that could be utilized by every professional employee on the hospital team, as implied by Beauchamp in his plea for total hospital effort in patient education.[1]

The Place of Psychological Tests and Vocational Information

Where does aptitude testing fit into the picture? Testing is indicated only when it can answer a question for the doctor or the patient, or counselor, or all of them. A psychological test is a systematic procedure for comparing the behavior of two or more persons. "That there aptitude test that'll tell me what I'm best suited for" just doesn't exist. No test can replace logical thinking, but many tests can yield helpful information with which to think. Psychological tests and measurements relate to vocational "diagnosis" in somewhat the same fashion that medical tests and measurements relate to disease diagnosis. The I.Q. Score, a finger dexterity test score, or an interest measurement are useful pieces of vocational information, just as tuberculin tests, pulse rates, or body temperatures are essential pieces of medical information.

Testing can also be a useful aid in obtaining a personality description which may assist the staff in planning treatment and rehabilitation programs for many patients. It can be a screen for early detection of many individuals who need help in personal adjustment. Testing is an aid; it cannot replace clinical interviewing, but only supplement it. Tests can sometimes be useful interviewing aids, like catalysts in the human interaction of the interview. Tests can be great timesavers in gathering some kinds of information which might be obtained through interviews only at greater time expense.

Vocational "diagnoses" and personality descriptions can be and often are rejected by the patient just as disease diagnoses are sometimes rejected. The individual can shop around for the answer he wants, and often does. The charlatan can then become the expert in the mind of the person to whom his advice appeals.

Test data must be combined with many other kinds of information that are also important in analyzing the vocational potential of an individual. Such things as the employment outlook for various classifications of workers, the accepted entrance channels to a given occupation, educational or age qualifications demanded by society or industry are highly important. Often factual information such as this is difficult for the patient to accept too, since it frequently destroys a vocational or rehabilitation plan that seems sound in every other respect, killing the plan that seemed to offer the patient security.

For example, a plan depending on initial part-time employment is frequently unsound, simply because such employment can rarely be found. Or a patient depending on a highly competitive field such as the fine arts is likely to be blocked by the reality of unemployment although this may be difficult to accept until he has passed the planning phase and comes face to face with the fact.

Many a patient has selected for himself a skilled trade goal, only to find that the route to attainment is through apprenticeship, and that apprentices are seldom accepted regardless of potential skill after the age of 20 or 25. Such facts are often resented and rejected by the patient. Occasionally an individual will take the attitude, "I'll show 'em, I can make the grade my way too!" And well he might, in an exceptional case; but success in planning vocational rehabilitation cannot depend on the exceptional case when surer ways are available.

Psychological testing and occupational information will be much more useful if the patient is prepared by adequate education to use them intelligently. Their usefulness is reduced greatly when vocational guidance is limited to testing only, with a terse advisement based largely on one interview subsequent to test analysis.

The basic problem of counseling, then, is not to test and advise, but to assist the individual to learn to adapt more efficiently. Tests are useful tools in the process. But the principal tool is the interview.

RESUMEN

El consejo vocacional para los tuberculosos no consiste sólo en el simple consejo para buscar determinada clase de trabajo. Debe ser un consejo psicológico con la mira de modificar la conducta del enfermo y sus capacidades par adaptarse a condiciones cambiantes y situaciones propias de problemas nuevos. Debe tratar de modificar muchas de las actitudes basícas que motivan la conducta.

Una actitud sistemática para este fin implica un programa—organizado de consejo psicológico en cooperación con personal médico, de enfermeras y de otros profesionales del hospital.

Ese consejo se describe como un esfuerzo de re-educación para ayudar a los enfermos y a resolver sus problemas más objetivamente y de manera más racional.

Se discute el lugar que las pruebas psicológicas y la información ocupacional desempeñan en el programa completo del consejo vocacional.

RESUME

Le service de reclassement professionnel du malade tuberculeux ne doit pas être un organisme où l'on donne simplement des conseils pour chercher une certaine catégorie de travail. Il doit devenir un organisme psychologique, ayant pour but de modifier la conduite du malade, et de développer sa faculté de s'adapter aux conditions modifiées et oux nouveaux problèmes que pose sa situation. Le but de cet organisme est de modifier beaucoup des attitudes fondamentales sur lesquelles le malade avait basé ses projets.

L'auteur demande que cet effort soit poursuivi systématiquement et intégré à un programme organisé de directives psychologiques, avec la collaboration du personnel médical, infirmier et des autres membres de la direction de l'Hôpital.

Ces directives psychologiques sont présentées comme un effort de rééducation pour aider les malades à voir eux-mêmes plus objectivement les problèmes qui les concernent et à pouvoir ainsi les résoudre plus rationnellement.

L'auteur discute la place du test psychologique et de l'enquête professionnelle dans le cadre du programme de reclassement professionnel.

ZUSAMMENFASSUNG

Berufsberatung für tuberkulöse Kranke ist nicht Sache eines einfachen Rates, eine bestimmte Art von Arbeit zu suchen. Sie muss eine psychologische Beratung sein mit dem Ziel, das Arbeitsschema des Kranken abzuwandeln und seine Fähigkeit zu entwickeln, sich ändernden Bedingungen und neuen Situationen mit neuen Problemen anzupassen. Sie muss danach streben, viele der grundlegenden Haltungen zu ändern, die sein Verhalten begründen.

Es wird eingetreten für die Bewerkstelligung einer systematischen Annäherung an diese Leistung durch eine organisierte Planung einer beratenden Psychologie in Zusammenarbeit mit dem ärztlichen, pflegerischen und anderem fachlichen Personal im Krankenhaus. Die Beratung wird beschrieben als ein Bemühen um Reedukation, um dem Kranken zu helfen sich selbst und seine Probleme seiner Situationen mehr objektiv zu sehen und dem zufolge bei der Lösung solcher Probleme mehr rationell zu handeln. Die Stellung einer psychologischen Prüfung und beruflichen Information in Beziehung zu dem gesamten Programm der Berufsberatung wird besprochen.

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Editorial

The Overall Effect of Antimicrobial Therapy on the Tuberculosis Program

Few ventures in the treatment of disease have had more far-reaching effects than the antimicrobial therapy of tuberculosis. Directly or indirectly, antimicrobial therapy is affecting every phase of the tuberculosis problem, from the biology of the micro-organism to the rehabilitation of patients.

Tuberculosis has always been noted for presenting many different manifestations in both the parasite and the host. Clinical tuberculosis in man ranges from acute to chronic, local to general, and benign to malignant. These variations are due to differences in both host and parasite, and each peculiar combination produces its own pattern. There are still wider variations in the animal kingdom at large. Practically every animal may contract the disease, and every animal species varies in its reactions to any particular strain of tubercle bacillus. It is also probable that factors within each species, such as age, race, sex, constitution, and so forth, influence the course and nature of the disease, as we know they do in human beings. The effect of antimicrobial therapy on this disease of many manifestations is as remarkable as it is far-reaching.

With the use of antimicrobials, great masses of bacterial populations are wiped out in a short time. The more active the growth of the bacilli, the more striking appears to be the effect of the antimicrobial agent. It seems quite possible that in some acute and fulminating cases, where all the bacilli are actively growing, there may be a complete sterilization of all bacilli present, as Steenken[1] has reported in his animal experimentations. In human tuberculosis many advanced cases have been made sputa bacillus free and remain so for two years or more, but only long observation and study, however, can prove how permanent are these observations. The study of resected lung lesions seems to be bearing out the experimental studies in animals.

In chronic disease, however, healing is slower and more uncertain, perhaps because of more inactive bacilli. In chronic cases or in those improperly treated, bacilli may be found in sputum or in the resected tissue indefinitely and seem to become reactivated after resistance in the bacilli has developed or after the cessation of treatment.

Antimicrobial therapy has up to the present time two significant drawbacks. One is due to the fact, just mentioned, that certain bacilli seem to slow down in their metabolic activity and even hibernate as sluggish bacilli or perhaps as granules, which many earlier workers described. During this state of "hibernation," drugs are less, or not at all, effective. These sluggish forms have been described recently by Canetti[2] as resting forms. Physiological experiments are cited to show that media devoid of many nutrient elements will slow down metabolic activity to a mere fraction

of the normal. The other drawback to antimicrobial therapy is due to that fundamental law of nature, the ability of living species to adapt to changing environment by the survival of mutants when changing environment threatens to exterminate the parent species. Molecular re-arrangements within the genes (genotypic changes) result in variations in the offspring that are better adapted to the new conditions.

The explanations of mutation as well as the more or less temporary changes in the cytoplasm due to the influence of environment (phenotypic changes) are not pertinent to this discussion any more than to say that geneticists have shown that mutation in each species takes place at a constant rate and the changes are entirely fortuitous. In keeping with the law of "Survival of the Fittest through Natural Selection" very few new forms survive. Most of them in the words of Darwin "shall be rigidly destroyed" because they are not properly adapted to the environment. The end product of the tubercle bacillus (as well as all other species of living organisms) is therefore the end result of a rigid selection of mutants to fit environments in which they were obliged to grow.

In spite of the fact that the tubercle bacillus has appeared to be a rather stable parasite many variations have been observed since its discovery, involving among other changes, variations in morphology, virulence, chromogenesis and gross colony formation.

In therapy, this phenomenon of mutation underlies the problem of bacterial resistance to antimicrobials. Resistance is the result of the survival and reproduction of mutants resistant to a given drug. Resistance of other bacteria to sulfa drugs and penicillin had been reported earlier, but Youmans[3] and his associates were the first to describe the development of resistance of tubercle bacilli to streptomycin.

Later it was shown that tubercle bacilli would develop resistance to all other antimicrobial agents, the degree and rate depending on the strain of bacilli, and the antimicrobial agent.

The resistance problem seemed to be limiting the usefulness of streptomycin and para-aminosalicylic acid until Donner[4] and his associates and later others gave the two drugs simultaneously. Various workers found that by combining other drugs the emergence of resistance could be greatly delayed. In many cases, the time before resistance developed was prolonged two or more fold. A greater number of cases became sputa bacillus free as a result of combined drug treatment. As a result, the whole field of antimicrobial therapy was widened in many directions. The end is not yet in sight, for other new agents are being discovered and Lattimer[5] has shown that with genito-urinary tuberculosis there may be added virtue in giving three drugs instead of two.

The explanation of these observations is not yet forthcoming, although Hobby[6] and her associates have suggested the possibility of a double mutation. There are probably othetr factors such as favorable additive effects when more than one drug is used. From present indications the explanation will depend upon future research. Recent studies in bacterial genetics have uncovered facts of great importance, with regard both to the

genetics of micro-organisms and to the fundamental laws of heredity. Everyone will await the interpretation of the interesting results with great expectation.

Changes in the bacilli, however, are only the beginning as far as tuberculosis is concerned. As might be supposed, alterations in the bacterial populations have a profound effect on pathology. Canetti has called attention to the fact that acute exudative alveolitis and perifocal reactions are rarely, if ever, found during effective antimicrobial therapy. These two acute reactions, which have always accompanied every tuberculous lesion and which cause many of the shadows appearing on x-ray, do not develop to any degree during successful antimicrobial therapy. Caseation already formed is slowed down and sometimes stopped, permitting resorption of the earlier type of lesions. In other cases, the progressive softening that leads to cavity formation does not occur. Auerbach[7] and his associates have shown that there is a clearing of the disease at the junction of the bronchus and cavity. Many times with re-epithelialization, Medlar[8] has shown that for one reason or another, most open cavities, even in minimal lesions, remain open for long intervals. Sweany and Seiler[9] have shown that there may be complete closure of many large cavities where there is a filling-in of space, first with granulation tissue and later with fibroblasts and connective tissue, to form large, dense, stellate scars. Canetti,[2] quoting several French authors, Thompson,[10] and others, report that some cavities become cleansed of infection and, instead of filling in with pus or healing over, become slick-walled sacs lined only with connective tissue. Where there are a large number of slick-walled cavities, the appearance is similar to that of a cystic lung or a bullous emphysema. Cavities less well sterilized of bacilli, or where there has been a closure of the bronchus entering the cavity, may become filled with inspissated pus. It may be said that in the pathology of the disease there are many changes, once common, which are now rarely seen and other changes once rarely seen are now common.

One of the greatest changes noted soon after streptomycin first came into use was that after some treatment the patient felt better. His toxicity seemed less. He began to eat more and soon gained weight. In many cases bacilli disappeared from the sputum and other favorable signs appeared. After a while, the x-ray shadows began to clear up. All these favorable changes were briefly augmented with each new drug and combination of drugs. Often morale of the patients became elevated so much that they were prone to judge their condition without advice of the physician and would take leave against medical advice. In spite of the great boon of the antimicrobials, the increased feeling of well-being posed new and sometimes serious problems, since many of the patients were not ready to go home in spite of their feeling of well-being. In earlier days, patients were more toxic and there were fewer who would risk their lives in any hasty misadventure.

More rapid amelioration of symptoms and improvement of the disease have therefore necessitated a complete change in methods of handling

patients. In dealing with patients much more leniency is permitted and practiced, but in spite of this, the leaving against medical advice problem is still serious. This situation has made necessary an increased emphasis on social service, occupational therapy, rehabilitation and other ancillary services in dealing with the increased number of patients who feel better but in the vast majority of instances are far from well. It has compelled the physician to temper leniency with sufficient discipline to avoid some of the booby traps along the way. Patients needing treatment because of previous lack of discipline now pose the greatest problem in treatment of tuberculosis. In addition, new types of behavior are making their appearance as the "bottom of the barrel" is approached in case finding. Most important in this latter group is the case with complications such as alcoholism and/or drug addiction. Cancer, senility and mental diseases also offer new obstacles. New methods, such as the use of commitment wards, are being developed in an attempt to save some of these patients.

One of the greatest changes arising from antimicrobial therapy has been in the field of surgery. Together with the more efficient use of blood and anesthesia, antimicrobials have permitted extension of resectional surgery to practically all patients with a comfortable pulmonary reserve. Mortality figures for resectional surgery have been reduced to levels that would have seemed impossible only a decade ago.

Finally there is the grand assault on the mortality from the disease as a whole which has, according to Anderson,[11] decreased 57 per cent within the last five years. Although the morbidity rate has only decreased about three per cent a year, it is apparently not yet free from the effects of increased case findings. The time is not far distant when the decrease in new infections will begin to show up in the statistics. There are already certain sections of the country where whole counties are practically free of clinical tuberculosis. Soon we may expect human tuberculosis to disappear county by county the country over, similar to, but slower than has taken place with bovine tuberculosis over the last few decades.

The chief problem still remaining will be that caused by soldiers, sailors and visitors to countries where tuberculosis is still common or even on the increase. Although the tuberculosis problem in government services will probably be present for a long time, continued application of the "seek, find and treat" method of control should end the threat in civilian life within a few decades.

Henry C. Sweany, M.D., F.C.C.P.

Complete reference list will appear in reprints.

The President's Page

In previous messages, I have discussed the programs of some of our councils and committees, forthcoming meetings, and other College activities. At this time, I would like to discuss one of the most important aspects of the College program, the splendid progress made by the College journal, *Diseases of the Chest.*

Our journal has achieved a position of world prominence in the specialty of chest diseases. Under the capable leadership of our Editorial Board, the College journal has progressed from a 32 page publication in 1935 to our present format of 144 pages issued monthly. An average of 110 pages are devoted to scientific material in each issue, or a total of 1,320 pages each year. The journal is a messenger which comes into your home or office each month to bring you the latest information on the most recent advances in diseases of the chest. Two volumes of the journal are published each year, complete with indices and contents pages. The subject matter of each issue includes the medical and surgical aspects of tuberculosis, non-tuberculous chest conditions, and cardiovascular diseases.

I would like to take this opportunity to pay tribute to the members of our Editorial Board for their devotion to a very time-consuming task: Drs. Andrew L. Banyai, William B. Bean, Richard H. Overholt, Henry C. Sweany, and Jay Arthur Myers, Chairman of the Board. They are to be congratulated for elevating the journal to its present high standing. I would also like to call your attention to the special features contained in the journal, such as the College News Section which brings our readers information and notices concerning international, national, and regional activities; College News Notes which carry items of interest concerning our members; the Calendar of Events which lists the places and dates of all College meetings and postgraduate courses; the Medical Service Bureau which carries positions wanted and available; the Medical Book Service Department, through which one may order any medical book, and last, but not least, the advertising pages which serve to inform you of new and useful ethical products used in the diagnosis and treatment of heart and lung diseases.

The summaries of scientific articles are translated into Spanish by Dr. Donato G. Alarcon, Mexico City, into German by Dr. Joachim Hein, Toensheide, and into French by Dr. Andre Meyer, Paris, and their respective associates. A great deal of international correspondence is required in the preparation of these summaries; however, the Editorial Board is of the opinion that through this procedure our readers are given the best possible translations.

The present circulation of *Diseases of the Chest* is 7,338 and is read by physicians in 91 countries and territories. There are no artificial barriers to prevent the distribution of *Diseases of the Chest* and the scientific information published in our journal is available to physicians everywhere. The medical profession is the finest example of a group dedicated to the free exchange of information among the peoples of the world. If all people would follow a program such as the medical profession has carried forward so successfully, there would be less cause for misunderstandings and mistrust. Physicians are attending international congresses in increasing numbers and are carrying out in a most democratic manner the "good-neighbor policy."

The American College of Chest Physicians has organized three international congresses on diseases of the chest during the past six years and the Fourth International Congress will be celebrated in Cologne, Germany, under the Presidency of Dr. Gerhard Domagk, August 19-23, 1956. Dr. Konrad Adenauer, Chancellor of West Germany, is Honorary President of this congress. An invitation is extended to all physicians to attend and I shall hope to have the pleasure of greeting you in Cologne.

The journal is your publication. Avail yourself of all it has to offer. No effort has been spared to bring you a medical journal that is interesting, attractive, and one of which you may be justly proud.

James H. Stygall

James H. Stygall, M.D.

FOURTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

The Cathedral of Cologne

The Council on International Affairs of the College is pleased to announce that the Secretariat for the Fourth International Congress on Diseases of the Chest to be held in Cologne, Germany, August 19-23, was officially opened in Cologne on February 1, 1956. Mrs. Anna Maria Maluquer-Wahl, who supervised the secretarial staff for the Third International Congress on Diseases of the Chest, held in Barcelona, Spain, in October, 1954, has been appointed Director of the Secretariat for the Congress to be held in Cologne this year. The address of the Secretariat is as follows: IV. Internationaler Kongress Für Erkrankungen der Thoraxorgane, Kongressbüro, Messeplatz, Verwaltungsgebaude, Köln, Deutschland.

Dr. Hans Ludes of Cologne, who is associated with Professor H. W. Knipping, Vice President of the Congress and Governor of the College for Nordrhein-Westfalen, has been appointed the Scientific Director of the Secretariat and will be in charge of the arrangements for the scientific sessions, motion picture programs, exhibits, etc.

At the present time the Secretariat is preparing registration forms for the Congress, which will be mailed to delegates throughout the world. It is recommended that all physicians planning to attend the Congress complete these forms and return them together with the appropriate registration fees, to the Secretariat at their earliest convenience.

The Congress Secretariat is also in complete charge of the assignment of hotel accommodations, and forms for this purpose will accompany the mailing of the registration applications. A deposit of DM 20.00 ($5.00 U. S. Currency) is required for each hotel reservation and must accompany the completed form.

The members of the program committee are working diligently on the preparation of the scientific program and it is anticipated that within the coming months, a tentative program will be published. The main themes of the program will include coronary disease, industrial diseases of the chest, tuberculosis, pulmonary function, cardiac function and tumors of the mediastinum. In addition to the formal presentations, a special panel of experts is being selected to discuss each of these subjects and there will also be free discussion from the floor. Special provision is being made for the presentation of papers dealing with topics unrelated to the main themes. Fireside Conferences will be held at the end of each daily session and will provide opportunity for open discussion of many subjects. Motion pictures on diseases of the chest will be shown throughout the days of the Congress. Two assembly halls will be equipped for simultaneous translation into the four official languages of the Congress, i. e., German, French, Spanish and English.

Various other functions are being planned in connection with the Congress, beginning with a brilliant Inaugural Session on Sunday evening, August 19. It is anticipated that Chancellor Konrad Adenauer, the Honorary President of the Congress, may present the opening address, and Professor Gerhard Domagk, the President of the Congress, will also speak at this impressive ceremony. The College Medal will be awarded to an outstanding scientist for meritorious achievement in the specialty of diseases of the chest and Certificates of Fellowship in the American College of Chest Physicians will be conferred upon new Fellows from throughout the world who are present for the Congress.

On Monday night, August 20, a symphony concert will be given and Tuesday, August 21, has been set aside for official receptions sponsored by the diplomatic corps of various countries. The closing banquet and grand ball will take place at the magnificent Messe Hall on Wednesday night, August 22. The sessions of the Congress will close at noon on Thursday, August 23, and a boat excursion on the beautiful Rhine River has been planned for that afternoon. There will also be a special program of ladies activities which will be of interest to the wives of the attending physicians.

The Executive Sessions of the Council on International Affairs of the American College of Chest Physicians will be held on Sunday afternoon, August 19 and on Thursday afternoon, August 23. All Regents, Governors, Chapter Officials and members of the Council have been requested to register in advance of the Congress for these important sessions.

On Friday, August 24, the delegates participating in the Post-Convention Tour will leave by special train for Coblenz, where the group will board a boat for the trip up the Rhine River to Wiesbaden. Subsequent visits will be made to Frankfurt, Heidelberg, Baden Baden and Munich, where tours, receptions and scientific programs are being arranged. The group will arrive in Vienna on Tuesday, August 30, where the International Bronchoesophagological Society will hold its Congress on Friday, Saturday and Sunday, August 31-September 1-2. A tour of Vienna and visits to historical places will be arranged, as well as an evening at the world famous opera. A limited number of seats will be reserved for delegates who wish to attend a performance at the Vienna Opera House.

The International Travel Service, Inc., Palmer House, Chicago 1, Illinois, has been appointed the official travel representative for the Congress. Tour folders have been sent to members of the College and additional information and reservations may be obtained by writing directly to them or to the Executive Offices of the College in Chicago.

22nd ANNUAL MEETING

Chicago will be host to the 22nd Annual Meeting of the American College of Chest Physicians which is to be held at the Hotel Sherman, June 7 through 10. An outstanding program is being prepared by the Committee on Scientific Program and a large attendance is anticipated. It is planned to publish the complete program in the April issue of *Diseases of the Chest*. All councils and committees of the College will hold their annual meetings in Chicago during this period. On page xiv you will find a convenient form for obtaining hotel reservations and it is recommended that this important detail be given your prompt attention.

The American Medical Association will hold its annual meeting in Chicago, June 11 through 15, and an interesting and instructive program will be presented in the Section on Diseases of the Chest. There will also be a large number of scientific exhibits of special interest to the chest specialist.

College Chapter News

ALABAMA CHAPTER

The third annual meeting of the Alabama Chapter will be held at the Thomas Jefferson Hotel, Birmingham, on April 18, just preceding the meeting of the Medical Association of Alabama. Dr. James C. Nash, Decatur, chapter Program Chairman, has arranged the following program:

2:00 p.m. "Congenital Cysts and Tumors of the Mediastinum: Radiological Aspects"
Edgar Little, New Orleans, Louisiana

"Congenital Cysts and Tumors of the Mediastinum: Surgical Aspects"
Duane Carr, Memphis, Tennessee

"Early Diagnosis of Bronchogenic Carcinoma"
Hollis Johnson, Nashville, Tennessee

"Pulmonary Emphysema and Cor Pulmonale: Physiological Treatment"
Ben Branscomb, Birmingham

Business session and election of officers

6:30 p.m. Dinner. (Reservations may be made prior to the meeting or at the time of registration for the afternoon session by contacting Dr. Kellie Joseph, Secretary-Treasurer, Woodward Building, Birmingham.)

8:00 p.m. Subject to be announced
Duane Carr, Memphis, Tennessee

"X-Ray Conference"
Duane Carr, Moderator
(Members and guests are encouraged to bring interesting or unusual chest x-ray films for interpretation and discussion at this conference.)

ARIZONA CHAPTER

The Arizona Chapter will hold its annual meeting at the San Marcos Hotel, Chandler, April 27, in conjunction with the meeting of the state medical association. The chapter will present the following program arranged under the chairmanship of Dr. Leslie B. Smith, Chapter President, Phoenix:

"Post-Operative Coronary Occlusions"
M. H. Delp, Kansas City, Kansas

"Mediastinal Tumors" and
"The Use of Body Section Radiography in the Study of the Chest"
Galen Tice, Kansas City, Kansas

"Carcinoma of the Lung—The Value of Cytological Studies During Radiation Therapy"
W. F. Har, Los Angeles, California

NEW ENGLAND STATES CHAPTER

At the regular monthly meeting of the New England States Chapter, held in Boston, Massachusetts, January 18, Dr. Andre Cournand, New York City, presented a lecture entitled "Physiological Principles in the Treatment of Chronic Pulmonary Emphysema."

TENNESSEE CHAPTER

The annual meeting of the Tennessee Chapter will be held at the Peabody Hotel, Memphis, April 10, in conjunction with the annual meeting of the Tennessee State Medical Association. The chapter will have a luncheon meeting followed by an afternoon scientific session.

MISSOURI CHAPTER

The annual meeting of the Missouri Chapter will be held on April 8 at the Statler Hotel, St. Louis, at the time of the meeting of the Missouri State Medical Association. Dr. Axel R. Gronau, Koch, Program Chairman, has arranged the following scientific session to be presented after a business meeting and luncheon at 12:00 noon:

"Surgical Palliation of Bronchogenic Carcinoma"
Thomas H. Burford, St. Louis
"Radiotherapy in Intrathoracic Neoplasms"
William B. Seaman, St. Louis
"Chemotherapy in Cancer with Special Reference to Thoracic Neoplasms"
Edward H. Reinhard, St. Louis
"Anesthetic Considerations in Patients for Chest Surgery with Impaired Cardiac, Renal, and Liver Function"
Edward O. Kraft, St. Louis
"Pilot Study of Oxamycin Toxicity"
Mario B. Pianetto, Koch

OHIO CHAPTER

The Ohio Chapter will hold its annual meeting in conjunction with the state medical society meeting at the Public Auditorium, Cleveland, April 10. The following program, arranged under the direction of Dr. Howard S. Van Ordstrand, Cleveland, will be presented:

10:00 a.m. "Is the Thoracic Lesion Malignant—Should We Operate?"
Julian Johnson, Philadelphia, Pennsylvania
"Some Pitfalls in Thoracic Diagnosis"
Bruce E. Douglass, Rochester, Minnesota
"Surgery for Chronic Pericardial Effusion: Biopsy and Pericardial Window"
Donald B. Effler, Cleveland
"High-Speed Cine-Fluorography for Angiocardiography during Cardiac Catheterization" (Film with comments by speaker)
F. Mason Sones, Jr., Cleveland

OKLAHOMA CHAPTER

The annual meeting of the Oklahoma Chapter will take place at the Veterans Administration Hospital, Oklahoma City, April 15, in conjunction with the Oklahoma Trudeau Society meeting. The program is as follows:

Morning Session
Moderator: James F. Hammarsten, Oklahoma City

9:00 a.m. "Ten Consecutive Admissions, Beginning May 1, 1955, Western Oklahoma Tuberculosis Sanatorium"
Glenn P. Dewberry, Clinton
"Ten Consecutive Discharges with Maximum Hospital Benefits Beginning October 1, 1955, Eastern Oklahoma Tuberculosis Sanatorium"
F. P. Baker, Talihina

12:00 noon Luncheon

Afternoon Session
Moderator: R. M. Shepard, Jr., Tulsa

1:30 p.m. "Ten Consecutive Pulmonary Resections for Tuberculosis, Veterans Administration Hospital, Oklahoma City"
C. M. Harvey, Oklahoma City
"Ten Consecutive Admissions to Children's Tuberculosis Ward, Talihina Medical Center"
Jan J. Waller, Talihina
Critique and Summary
William B. Tucker, Durham, North Carolina and
Donald L. Paulson, Dallas, Texas

OKLAHOMA CHAPTER—Continued

5:15 p.m. Business meeting
Evening Session
Presiding: Paul B. Lingenfelter, Clinton
6:00 p.m. Social Hour
7:00 p.m. Dinner (Regency Room, Skirvin Hotel)
"Current Evaluation of Antimicrobial Drugs in Tuberculosis"
William B. Tucker
"Indications for Pulmonary Resection in Tuberculosis"
Donald L. Paulson

TEXAS CHAPTER

The Texas Chapter will hold its annual meeting in the Terrace Room, Galvez Hotel, Galveston, Sunday, April 22, during the meeting of the state medical association. Dr. Alvis E. Greer, Houston, Program Chairman, has arranged the following program:

9:00 a.m. "Sarcoidosis"
J. Otis Armstrong, Dallas
"Medical Aspects of Mitral Stenosis"
Paul Thomas, Dallas
"Heart Disease of Pulmonary Origin"
George R. Herrmann, Galveston
"Results of Mitral Commissurotomy for Mitral Stenosis"
Robert R. Shaw, Donald L. Paulson, and John L. Kee, Dallas
"Differential Diagnosis of Intrathoracic Lesions"
Lawrence M. Shefts, San Antonio
12:00 noon Luncheon and business meeting
2:00 p.m. "Systemic Mycoses"
Emma Moss, New Orleans, Louisiana
"Histoplasmosis and Blastomycosis"
Edward P. Cawley, Charlottesville, Virginia
"Principles of Inhalational Therapy"
Maurice S. Segal, Boston, Massachusetts
"Primary Tuberculosis in Childhood—Presentation, Course, Treatment, and Sequelae"
John Derham, Liverpool, England
"Conference on X-ray and Pathological Correlation of Pulmonary Lesions"
Walter J. Stork, Houston

Dr. Daniel E. Jenkins, Houston, will present his exhibit entitled "Value of Drug Therapy in Tuberculosis" at the meeting.

WISCONSIN CHAPTER

The annual meeting of the Wisconsin Chapter will be held at the Schroeder Hotel, Milwaukee, April 29. Dr. Leon H. Hirsh, Milwaukee, has arranged the following scientific program:

2:00 p.m. "Recent Advances in the Management of Asthma"
G. A. Koelsche, Rochester, Minnesota
"Pulmonary Manifestations of Collagen Diseases"
Joseph F. Kuzma, Milwaukee
"Atrial Fibrillation—Reversion to Sinus Rhythm"
Ray W. Kissane, Columbus, Ohio
"The Significance of Isolated Nodular Lesions in the Chest X-ray"
Edwin R. Levine, Chicago, Illinois
"The Treatment of Congestive Heart Failure"
John F. Briggs, St. Paul, Minnesota
Panel Discussion of Questions from the Floor
Moderator: Mischa J. Lustok, Milwaukee
Participants: G. A. Koelsche
Joseph F. Kuzma
Ray W. Kissane
Edwin R. Levine
John F. Briggs

PHILIPPINE CHAPTER

Members of the Philippine Chapter elected the following officers at their recent annual meeting:

President:	Laureano D. Bautista, Quezon City
President-Elect:	Godofredo Hebron, Manila
Vice-President:	Adolfo Baviera, Quezon City
Secretary-Treasurer:	Priscilla Tablan, Quezon City (re-elected)

On December 21, the chapter held a scientific meeting at the Quezon Institute, Quezon City. Dr. Cirilo Santos, outgoing president of the chapter, presided, and Dr. Miguel Canizares, Regent of the College for the Philippines, introduced the guest of honor, Dr. I. C. Fang, Regional Director of the Western Pacific Area, World Health Organization. Dr. Fang presented the newly elected officers of the chapter. Following an inaugural address by Dr. Laureano Bautista, Drs. Enrique Garcia, Angel I. Reyes, Rafael A. Garcia, and Regelio Teodico of the Department of Surgery, Quezon Institute, spoke on "Mediastinal Tumors."

Obituary

ALFRED L. KRUGER
1911 - 1955

It is with the deepest regret that the members of the Virginia Chapter of the American College of Chest Physicians record the death of Dr. Alfred L. Kruger, Fellow, American College of Chest Physicians, of Norfolk, Virginia, who passed away December 25, 1955 of an acute attack of myocardial infarction, it being the third attack in two years.

Dr. Kruger was born on February 16, 1911. He took his preliminary education in the Norfolk public schools. He received his academic and medical training at the University of Virginia, where he graduated in 1935 with honor. He served as President of the social fraternity Phi Alpha and was a member of Phi Delta Epsilon, a medical fraternity.

After graduation, Dr. Kruger accepted a rotating internship for eighteen months at the Jersey City Medical Center. He then served as houseship in x-ray for six months. After this, he served as resident physician at the Hudson County Tuberculosis Hospital, which was later named the Berthold S. Pollak Hospital of Chest Diseases. During this time he also took postgraduate work at Johns Hopkins Hospital and New York Postgraduate Hospital.

He served as Lieutenant in the United States Air Force during World War II, being stationed at Kessler Field, Biloxi, Mississippi, for a tour of four years.

On September 18, 1938, Dr. Kruger married Miss Louise Pollak of New Jersey, who survives. They have two children, Virginia Louise, age fifteen and Alfred L. Kruger, Jr., age eleven.

After being discharged from the Air Force in February, 1946, Dr. Kruger returned to Norfolk to start his life's work. He limited this work to internal medicine, paying special attention to diseases of the chest. He was a member of the Norfolk County Medical Society of Virginia, the American Medical Association, Diplomate of the American Board of Internal Medicine, Fellow of the American College of Physicians, and a Fellow of the American College of Chest Physicians. He was Governor for Virginia of this organization since July, 1955.

Dr. Kruger was also a member of the Trudeau Society, The Southern Medical Association and Seaboard Medical Society. He was Chief of Thoracic Diseases at Norfolk General Hospital, a member of the staff of De Paul Hospital and Leigh Memorial Hospital, and Chairman of the Medical Board of Grandy Sanatorium (a municipal hospital).

Dr. Kruger was a member of Ohef Sholom Temple, President of B'nai B'rith Lodge 1195, a Mason and a Shriner.

Dr. A. L. Kruger was a promising young physician, very popular among physicians and his patients and beloved by his family. His demise at the age of forty-four was very untimely. He will be missed by many.

C. Lydon Harrell, M.D.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

22nd Annual Meeting, American College of Chest Physicians
Hotel Sherman, Chicago, Illinois, June 7-10, 1956

Fourth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Cologne, Germany, August 19-23, 1956

POSTGRADUATE COURSES

9th Annual Postgraduate Course on Diseases of the Chest
Bellevue-Stratford Hotel, Philadelphia, March 19-23, 1956

CHAPTER MEETINGS

Missouri Chapter, St. Louis, April 8, 1956
Tennessee Chapter, Memphis, April 10, 1956
Ohio Chapter, Cleveland, April 10, 1956
Oklahoma Chapter, Oklahoma City, April 15, 1956
Alabama Chapter, Birmingham, April 18, 1956
Texas Chapter, Galveston, April 22, 1956
Arkansas Chapter, Little Rock, April 22, 1956
Arizona Chapter, Chandler, April 27, 1956
California Chapter, Los Angeles, April 28, 1956
Wisconsin Chapter, Milwaukee, April 29, 1956

MEDICAL SERVICE BUREAU

Position Wanted

Anesthesiologist, M.D., age 45, licensed in California, seeks full-time position in Southern California hospital. Ten years specialty experience, of which seven devoted to chest and cancer work in large privately endowed institution. Please address inquiries to Box 284B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Positions Available

Full-time physicians wanted for new 440-bed tuberculosis division of large general hospital in east; available immediately; associated with two medical schools for teaching purposes; opportunity for research; complete surgical and pathological facilities; salary governed by background and experience. Please address inquiries to Box 286A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

The Veterans Administration Hospital, Downey, Illinois, has openings for tuberculosis specialists on its staff for the treatment of patients suffering from concurrent psychiatric and tuberculosis disorders. Salary based on qualifications of physicians employed, ranging from $7,570 to $11,610 per year. Contact W. K. Freeman, M.D., Manager, VA Hospital, Downey, Illinois.

Immediate opening for staff and resident physicians in tuberculosis hospital. Service includes a great deal of internal medicine and chest surgery. Approved pulmonary disease residency. Excellent salary, plus maintenance if desired. Eligibility for state license required. Write: Superintendent, Sunnyside Sanatorium, Indianapolis 26, Indiana.

Tuberculosis physicians wanted to staff new 200-bed, air-conditioned sanatorium, opening July 1, 1956. Adjacent Medical College of Virginia and its hospital; complete facilities available for chest surgery, surgical and other consultation; out-patient clinics; occupational therapy; rehabilitation; opportunities for teaching and research; eligibility for licensure in Virginia required; all positions covered by social security, state retirement, vacation, and sick-leave:

Medical Director: position open now. Salary range $12,000 to $13,128; five or more years' clinical experience in tuberculosis, four of which served in approved sanatorium and one year in a senior grade; one or more additional years satisfactory experience may be substituted for sanatorium service; Board certification internal medicine desirable.

Physician B (3): Salary range $9,600 to $11,472; two years experience in approved tuberculosis sanatorium or two years in clinic or office practice under supervision of competent chest specialist; two years general practice may be substituted for one year sanatorium or non-sanatorium specialized chest disease experience.

Physician A (1): Salary range $8,400 to $9,168.

Apply to Mack I. Shanholtz, M.D., State Health Commissioner, Department of Health, Richmond 19, Virginia.

Clinical Director wanted to perform executive and professional functions for 550-bed hospital in Rio Grande Valley. Excellent opportunity to assist in developing new state tuberculosis hospital. Preference given applicants with management ability and some tuberculosis experience. Annual salary $10,600 including emoluments. Please address replies to: Dr. Ellison F. White, Superintendent, Harlingen State Tuberculosis Hospital, Harlingen, Texas, listing details of training and experience.

Tuberculosis Director wanted to work out of Central Office in Austin (Texas) supervising state-wide program for tuberculosis which includes five state tuberculosis hospitals. This position provides opportunity to use professional and executive abilities. Annual salary $15,000. Only doctors with national reputation in tuberculosis need apply. Please send resume of training and experience to: Dr. James A. Bethea, Executive Director, Board for Texas State Hospitals and Special Schools, Box S, Capitol Station, Austin, Texas.

Clinical Director wanted. Excellent possibilities for clinical director and branch manager of 400-bed branch hospital in hill country of Texas. Preference given applicants with management ability and tuberculosis experience. Annual salary and emoluments $10,300. This position provides opportunity to use initiative. Please send resume of training and experience to: Dr. W. L. Peterson, Superintendent, San Antonio State Tuberculosis Hospital, San Antonio, Texas.

Director of tuberculosis nursing wanted. Outstanding opportunity in Central Office of Board of Texas State Hospitals and Special Schools in Austin for progressive registered nurse with heavy management experience. In this position, assist in directing nursing activities in five state tuberculosis hospitals. May provide opportunity to use initiative and management experience. Annual salary $6,300. Address replies to: Dr. James A. Bethea, Executive Director, Board for Texas State Hospitals and Special Schools, Box S, Capitol Station, Austin, Texas, listing details of training and experience.

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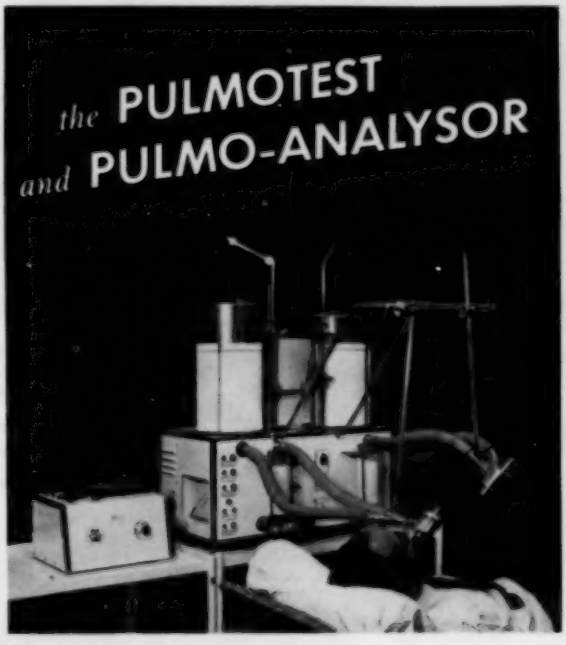
- Bronchospirometry: Oxygen consumption and Vital Capacity of each lung
- CO_2 concentration of expired gases

UNIT TO BE SHOWN

American College of Chest Physicians: June 6-10, Chicago



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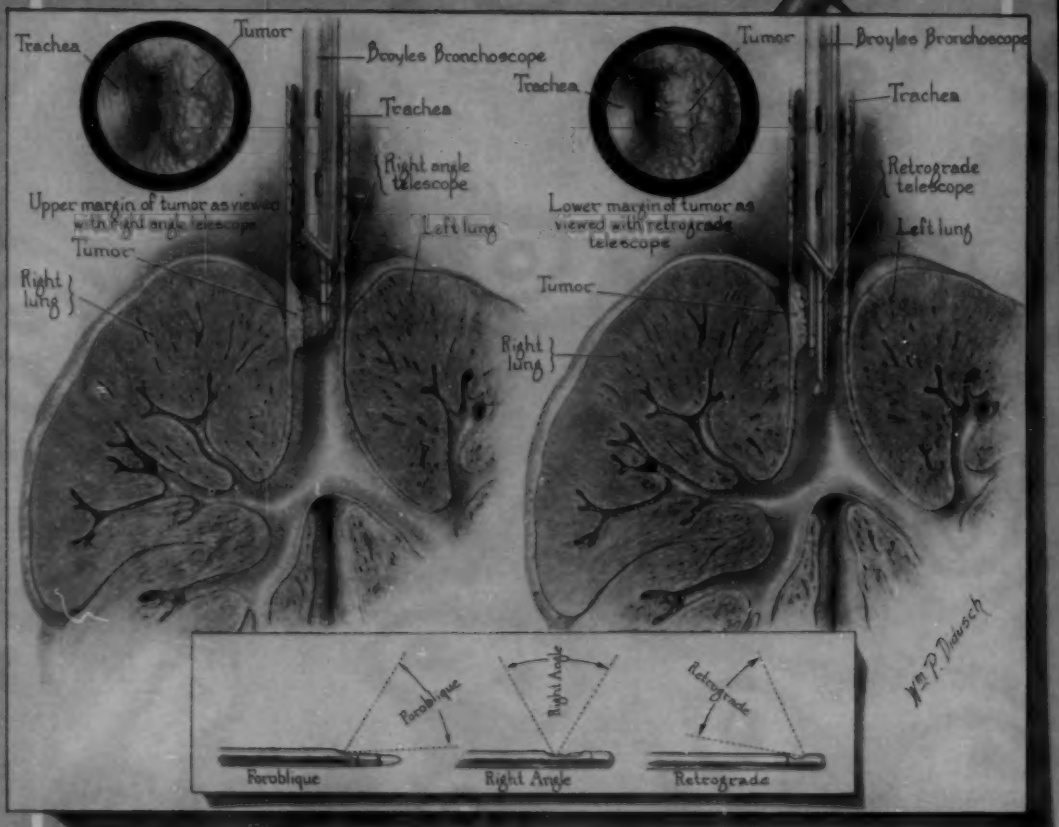

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